

**TARGETED CHROMOSOMAL GENOMIC ALTERATIONS
WITH MODIFIED SINGLE STRANDED OLIGONUCLEOTIDES**

Field Of The Invention

The technical field of the invention is oligonucleotide-directed repair or alteration of genetic information using novel chemically modified oligonucleotides. Such genetic information is preferably from a eukaryotic organism, i.e. a plant, animal or fungus.

Background Of The Invention

A number of methods have been developed specifically to alter the sequence of an isolated DNA in addition to methods to alter directly the genomic information of various plants, fungi and animals, including humans ("gene therapy"). The latter methods generally include the use of viral or plasmid vectors carrying nucleic acid sequences encoding partial or complete portions of a particular protein which is expressed in a cell or tissue to effect the alteration. The expression of the particular protein then results in the desired phenotype. For example, retroviral vectors containing a transgenic DNA sequence allowing for the production of a normal CFTR protein when administered to defective cells are described in U.S. Patent 5,240,846. Others have developed different "gene therapy vectors" which include, for example, portions of adenovirus (Ad) or adeno-associated virus (AAV), or other viruses. The virus portions used are often long terminal repeat sequences which are added to the ends of a transgene of choice along with other necessary control sequences which allow expression of the transgene. See U.S. Patents 5,700,470 and 5,139,941. Similar methods have been developed for use in plants. See, for example, U.S. Patent 4,459,355 which describes a method for transforming plants with a DNA vector and U.S. Patent 5,188,642 which describes cloning or expression vectors containing a transgenic DNA sequence which when expressed in plants confers resistance to the herbicide glyphosate. The use of such transgene vectors in any eukaryotic organism adds one or more exogenous copies of a gene, which gene may be foreign to the host, in a usually random fashion at one or more integration sites of the organism's genome at some frequency. The gene which was originally present in the genome, which may be a normal allelic variant, mutated, defective, and/or functional, is retained in the genome of the host.

These methods of gene correction are problematic in that complications which can compromise the health of the recipient, or even lead to death, may result. One such problem is that insertion of exogenous nucleic acid at random location(s) in the genome can have deleterious effects. Another problem with such systems includes the addition of unnecessary and unwanted genetic material to the genome of the recipient, including, for example, viral or other vector remnants, control sequences required to allow production of the transgene protein, and reporter genes or resistance markers. Such remnants and added sequences may have presently unrecognized consequences, for example, involving genetic rearrangements of the recipient genomes. Other problems associated with these types of traditional gene therapy methods include autoimmune suppression of cells expressing an inserted gene due to the presence of foreign antigens. Concerns have also been raised with consumption, especially by humans, of plants containing exogenous genetic material.

More recently, simpler systems involving poly- or oligo- nucleotides have been described for use in the alteration of genomic DNA. These chimeric RNA-DNA oligonucleotides, requiring contiguous RNA and DNA bases in a double-stranded molecule folded by complementarity into a double hairpin conformation, have been shown to effect single basepair or frameshift alterations, for example, for mutation or repair of plant or animal genomes. See, for example, WO 99/07865 and U.S. Patent 5,565,350. In the chimeric RNA-DNA oligonucleotide, an uninterrupted stretch of DNA bases within the molecule is required for sequence alteration of the targeted genome while the obligate RNA residues are involved in complex stability. Due to the length, backbone composition, and structural configuration of these chimeric RNA-DNA molecules, they are expensive to synthesize and difficult to purify. Moreover, if the RNA-containing strand of the chimeric RNA-DNA oligonucleotide is designed so as to direct gene conversion, a series of mutagenic reactions resulting in nonspecific base alteration can result. Such a result compromises the utility of such a molecule in methods designed to alter the genomes of plants and animals, including in human gene therapy applications.

Alternatively, other oligo- or poly- nucleotides have been used which require a triplex forming, usually polypurine or polypyrimidine, structural domain which binds to a DNA helical duplex through Hoogsteen interactions between the major groove of the DNA duplex and the oligonucleotide. Such oligonucleotides may have an additional DNA reactive moiety, such as psoralen, covalently linked to the oligonucleotide. These reactive moieties function as effective intercalation agents, stabilize the formation of a triplex and can be mutagenic. Such agents may be required in order to stabilize the triplex forming domain of the oligonucleotide with the DNA double helix if the Hoogsteen interactions from the oligonucleotide/target base composition are insufficient. See, e.g., U.S. Patent 5,422,251. The utility of

these oligonucleotides for directing gene conversion is compromised by a high frequency of nonspecific base changes.

In more recent work, the domain for altering a genome is linked or tethered to the triplex forming domain of the bi-functional oligonucleotide, adding an additional linking or tethering functional domain to the oligonucleotide. See, e.g., Culver et al., Nature Biotechnology 17: 989-93 (1999). Such chimeric or triplex forming molecules have distinct structural requirements for each of the different domains of the complete poly- or oligo-nucleotide in order to effect the desired genomic alteration in either episomal or chromosomal targets.

Other genes, e.g. CFTR, have been targeted by homologous recombination using duplex fragments having several hundred basepairs. See, e.g., Kunzelmann et al., Gene Ther. 3:859-867 (1996). Early experiments to mutagenize an antibiotic resistance indicator gene by homologous recombination used an unmodified DNA oligonucleotide with no functional domains other than a region of complementary sequence to the target. See Campbell et al., New Biologist 1: 223-227 (1989). These experiments required large concentrations of the oligonucleotide, exhibited a very low frequency of episomal modification of a targeted exogenous plasmid gene not normally found in the cell and have not been reproduced. However, as shown in the examples herein, we have observed that an unmodified DNA oligonucleotide can convert a base at low frequency which is detectable using the assay systems described herein.

Artificial chromosomes can be useful for the screening purposes identified herein. These molecules are man-made linear or circular DNA molecules constructed from essential cis-acting DNA sequence elements that are responsible for the proper replication and partitioning of natural chromosomes (Murray et al., 1983). The essential elements are: (1) Autonomous Replication Sequences (ARS), (2) Centromeres, and (3) Telomeres.

Yeast artificial chromosomes (YACs) allow large genomic DNA to be modified and used for generating transgenic animals [Burke et al., Science 236:806; Peterson et al., Trends Genet. 13:61 (1997); Choi, et al., Nat. Genet. 4:117-223 (1993), Davies, et al., Biotechnology 11:911-914 (1993), Matsuura, et al., Hum. Mol. Genet., 5:451-459 (1996), Peterson et al., Proc. Natl. Acad. Sci., 93:6605-6609 (1996); and Schedl, et al., Cell, 86:71-82 (1996)]. Other vectors also have been developed for the cloning of large segments of mammalian DNA, including cosmids, and bacteriophage P1 [Sternberg et al., Proc. Natl. Acad. Sci. U.S.A., 87:103-107 (1990)]. YACs have certain advantages over these alternative large capacity cloning vectors [Burke et al., Science, 236:806-812 (1987)]. The

maximum insert size is 35-30 kb for cosmids, and 100 kb for bacteriophage P1, both of which are much smaller than the maximal insert for a YAC.

An alternative to YACs are *E. coli* based cloning systems based on the *E. coli* fertility factor that have been developed to construct large genomic DNA insert libraries. They are bacterial artificial chromosomes (BACs) and P-1 derived artificial chromosomes (PACs) [Mejia et al., Genome Res. 7:179-186 (1997); Shizuya et al., Proc. Natl. Acad. Sci. 89:8794-8797 (1992); Ioannou et al., Nat. Genet. 6:84-89 (1994); Hosoda et al., Nucleic Acids Res. 18:3863 (1990)]. BACs are based on the *E. coli* fertility plasmid (F factor); and PACs are based on the bacteriophage P1. These vectors propagate at a very low copy number (1-2 per cell) enabling genomic inserts up to 300 kb in size to be stably maintained in recombination deficient hosts. Furthermore, the PACs and BACs are circular DNA molecules that are readily isolated from the host genomic background by classical alkaline lysis [Birnboim et al., Nucleic Acids Res. 7:1513-1523 (1979)].

Oligonucleotides designed for use in the alteration of genetic information are significantly different from oligonucleotides designed for antisense approaches. For example, antisense oligonucleotides are perfectly complementary to and bind an mRNA strand in order to modify expression of a targeted mRNA and are used at high concentration. As a consequence, they are unable to produce a gene conversion event by either mutagenesis or repair of a defect in the chromosomal DNA of a host genome. Furthermore, the backbone chemical composition used in most oligonucleotides designed for use in antisense approaches renders them inactive as substrates for homologous pairing or mismatch repair enzymes and the high concentrations of oligonucleotide required for antisense applications can be toxic with some types of nucleotide modifications. In addition, antisense oligonucleotides must be complementary to the mRNA and therefore, may not be complementary to the other DNA strand or to genomic sequences that span the junction between intron sequence and exon sequence.

A need exists for simple, inexpensive oligonucleotides capable of producing targeted alteration of genetic material such as those described herein as well as methods to identify optimal oligonucleotides that accurately and efficiently alter target DNA.

Summary Of The Invention

Novel, modified single-stranded nucleic acid molecules that direct gene alteration in plants, fungi and animals are identified and the efficiency of alteration is analyzed both *in vitro* using a cell-free extract assay and *in vivo* using a yeast cell system. The alteration in an oligonucleotide of the invention may comprise an insertion, deletion, substitution, as well as any combination of these. Site

specific alteration of DNA is not only useful for studying function of proteins *in vivo*, but it is also useful for creating animal models for human disease, and in gene therapy. As described herein, oligonucleotides of the invention target directed specific gene alterations in genomic double-stranded DNA cells. The target DNA can be normal, cellular chromosomal DNA, extrachromosomal DNA present in cells in different forms including, e.g., mammalian artificial chromosomes (MACs), PACs from P-1 vectors, yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), plant artificial chromosomes (PLACs), as well as episomal DNA, including episomal DNA from an exogenous source such as a plasmid or recombinant vector. Many of these artificial chromosome constructs containing human DNA can be obtained from a variety of sources, including, e.g., the Whitehead Institute, and are described, e.g., in Cohen et al., *Nature* 336:698-701 (1993) and Chumakov, et al., *Nature* 377:174-297 (1995). The target DNA may be transcriptionally silent or active. In a preferred embodiment, the target DNA to be altered is the non-transcribed strand of a genomic DNA duplex.

The low efficiency of gene alteration obtained using unmodified DNA oligonucleotides is believed to be largely the result of degradation by nucleases present in the reaction mixture or the target cell. Although different modifications are known to have different effects on the nuclease resistance of oligonucleotides or stability of duplexes formed by such oligonucleotides (see, e.g., Koshkin et al., *J. Am. Chem. Soc.*, 120:13252-3), we have found that it is not possible to predict which of any particular known modification would be most useful for any given alteration event, including for the construction of gene conversion oligonucleotides, because of the interaction of different as yet unidentified proteins during the gene alteration event. Herein, a variety of nucleic acid analogs have been developed that increase the nuclease resistance of oligonucleotides that contain them, including, e.g., nucleotides containing phosphorothioate linkages or 2'-O-methyl analogs. We recently discovered that single-stranded DNA oligonucleotides modified to contain 2'-O-methyl RNA nucleotides or phosphorothioate linkages can enable specific alteration of genetic information at a higher level than either unmodified single-stranded DNA or a chimeric RNA/DNA molecule. See priority applications incorporated herein in their entirety; see also Gamper et al., *Nucleic Acids Research* 28: 4332-4339 (2000). We also found that additional nucleic acid analogs which increase the nuclease resistance of oligonucleotides that contain them, including, e.g., "locked nucleic acids" or "LNAs", xylo-LNAs and L-ribo-LNAs; see, for example, Wengel & Nielsen, WO 99/14226; Wengel, WO 00/56748 and Wengel, WO 00/66604; also allow specific targeted alteration of genetic information.

The assay allows for determining the optimum length of the oligonucleotide, optimum sequence of the oligonucleotide, optimum position of the mismatched base or bases, optimum chemical

modification or modifications, optimum strand targeted for identifying and selecting the most efficient oligonucleotide for a particular gene alteration event by comparing to a control oligonucleotide. Control oligonucleotides may include a chimeric RNA-DNA double hairpin oligonucleotide directing the same gene alteration event, an oligonucleotide that matches its target completely, an oligonucleotide in which all linkages are phosphorothiolated, an oligonucleotide fully substituted with 2'-O-methyl analogs or an RNA oligonucleotide. Such control oligonucleotides either fail to direct a targeted alteration or do so at a lower efficiency as compared to the oligonucleotides of the invention. The assay further allows for determining the optimum position of a gene alteration event within an oligonucleotide, optimum concentration of the selected oligonucleotide for maximum alteration efficiency by systematically testing a range of concentrations, as well as optimization of either the source of cell extract by testing different organisms or strains, or testing cells derived from different organisms or strains, or cell lines. Using a series of single-stranded oligonucleotides, comprising all RNA or DNA residues and various mixtures of the two, several new structures are identified as viable molecules in nucleotide conversion to direct or repair a genomic mutagenic event. When extracts from mammalian, plant and fungal cells are used and are analyzed using a genetic readout assay in bacteria, single-stranded oligonucleotides having one of several modifications are found to be more active than a control RNA-DNA double hairpin chimera structure when evaluated using an *in vitro* gene repair assay. Similar results are also observed *in vivo* using yeast, mammalian, rodent, monkey, human and embryonic cells, including stem cells. Molecules containing various lengths of modified bases were found to possess greater activity than unmodified single-stranded DNA molecules.

Detailed Description Of The Invention

The present invention provides oligonucleotides having chemically modified, nuclease resistant residues, preferably at or near the termini of the oligonucleotides, and methods for their identification and use in targeted alteration of genetic material, including gene mutation, targeted gene repair and gene knockout. The oligonucleotides are preferably used for mismatch repair or alteration by changing at least one nucleic acid base, or for frameshift repair or alteration by addition or deletion of at least one nucleic acid base. The oligonucleotides of the invention direct any such alteration, including gene correction, gene repair or gene mutation and can be used, for example, to introduce a polymorphism or haplotype or to eliminate ("knockout") a particular protein activity.

The oligonucleotides of the invention are designed as substrates for homologous pairing and repair enzymes and as such have a unique backbone composition that differs from chimeric RNA-

DNA double hairpin oligonucleotides, antisense oligonucleotides, and/or other poly- or oligo-nucleotides used for altering genomic DNA, such as triplex forming oligonucleotides. The single-stranded oligonucleotides described herein are inexpensive to synthesize and easy to purify. In side-by-side comparisons, an optimized single-stranded oligonucleotide comprising modified residues as described herein is significantly more efficient than a chimeric RNA-DNA double hairpin oligonucleotide in directing a base substitution or frameshift mutation in a cell-free extract assay.

We have discovered that single-stranded oligonucleotides having a DNA domain surrounding the targeted base, with the domain preferably central to the poly- or oligo-nucleotide, and having at least one modified end, preferably at the 3' terminal region are able to alter a target genetic sequence and with an efficiency that is higher than chimeric RNA-DNA double hairpin oligonucleotides disclosed in US Patent 5,565,350. Oligonucleotides of the invention can efficiently be used to introduce targeted alterations in a genetic sequence of DNA in the presence of human, animal, plant, fungal (including yeast) proteins and in cultured cells of human liver, lung, colon, cervix, kidney, epithelium and cancer cells and in monkey, hamster, rat and mouse cells of different types, as well as embryonic stem cells. Cells for use in the invention include, e.g., fungi including *S. cerevisiae*, *Ustilago maydis* and *Candida albicans*, mammalian, mouse, hamster, rat, monkey, human and embryonic cells including stem cells. The DNA domain is preferably fully complementary to one strand of the gene target, except for the mismatch base or bases responsible for the gene alteration or conversion events. On either side of the preferably central DNA domain, the contiguous bases may be either RNA bases or, preferably, are primarily DNA bases. The central DNA domain is generally at least 8 nucleotides in length. The base(s) targeted for alteration in the most preferred embodiments are at least about 8, 9 or 10 bases from one end of the oligonucleotide.

According to certain embodiments, the termini of the oligonucleotides of the present invention comprise phosphorothioate modifications, LNA backbone modifications, or 2'-O-methyl base analogs, or any combination of these modifications. Oligonucleotides comprising 2'-O-methyl or LNA analogs are a mixed DNA/RNA polymer. These oligonucleotides are, however, single-stranded and are not designed to form a stable internal duplex structure within the oligonucleotide. The efficiency of gene alteration is surprisingly increased with oligonucleotides having internal complementary sequence comprising phosphorothioate modified bases as compared to 2'-O-methyl modifications. This result indicates that specific chemical interactions are involved between the converting oligonucleotide and the proteins involved in the conversion. The effect of other such chemical interactions to produce nuclease resistant termini using modifications other than LNA, phosphorothioate linkages, or 2'-O-methyl analog

incorporation into an oligonucleotide can not yet be predicted because the proteins involved in the alteration process and their particular chemical interaction with the oligonucleotide substituents are not yet known and cannot be predicted.

In the examples, correcting oligonucleotides of defined sequence are provided for correction of genes mutated in human diseases. In the tables of these examples, the oligonucleotides of the invention are not limited to the particular sequences disclosed. The oligonucleotides of the invention include extensions of the appropriate sequence of the longer 120 base oligonucleotides which can be added base by base to the smallest disclosed oligonucleotides of 17 bases. Thus the oligonucleotides of the invention include for each correcting change, oligonucleotides of length 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, or 120 with further single-nucleotide additions up to the longest sequence disclosed. Moreover, the oligonucleotides of the invention do not require a symmetrical extension on either side of the central DNA domain. Similarly, the oligonucleotides of the invention as disclosed in the various tables for correction of human diseases contain phosphorothioate linkages, 2'-O-methyl analogs or LNAs or any combination of these modifications just as the assay oligonucleotides do.

The present invention, however, is not limited to oligonucleotides that contain any particular nuclease resistant modification. Oligonucleotides of the invention may be altered with any combination of additional LNAs, phosphorothioate linkages or 2'-O-methyl analogs to maximize conversion efficiency. For oligonucleotides of the invention that are longer than about 17 to about 25 bases in length, internal as well as terminal region segments of the backbone may be altered. Alternatively, simple fold-back structures at each end of a oligonucleotide or appended end groups may be used in addition to a modified backbone for conferring additional nuclease resistance.

The different oligonucleotides of the present invention preferably contain more than one of the aforementioned backbone modifications at each end. In some embodiments, the backbone modifications are adjacent to one another. However, the optimal number and placement of backbone modifications for any individual oligonucleotide will vary with the length of the oligonucleotide and the particular type of backbone modification(s) that are used. If constructs of identical sequence having phosphorothioate linkages are compared, 2, 3, 4, 5, or 6 phosphorothioate linkages at each end are preferred. If constructs of identical sequence having 2'-O-methyl base analogs are compared, 1, 2, 3 or 4

analog are preferred. The optimal number and type of backbone modifications for any particular oligonucleotide useful for altering target DNA may be determined empirically by comparing the alteration efficiency of the oligonucleotide comprising any combination of the modifications to a control molecule of comparable sequence using any of the assays described herein. The optimal position(s) for
5 oligonucleotide modifications for a maximally efficient altering oligonucleotide can be determined by testing the various modifications as compared to control molecule of comparable sequence in one of the assays disclosed herein. In such assays, a control molecule includes, e.g., a completely 2'-O-methyl substituted molecule, a completely complementary oligonucleotide, or a chimeric RNA-DNA double hairpin.

10 Increasing the number of phosphorothioate linkages, LNAs or 2'-O-methyl bases beyond the preferred number generally decreases the gene repair activity of a 25 nucleotide long oligonucleotide. Based on analysis of the concentration of oligonucleotide present in the extract after different time periods of incubation, it is believed that the terminal modifications impart nuclease resistance to the oligonucleotide thereby allowing it to survive within the cellular environment. However, this may not be the only
15 possible mechanism by which such modifications confer greater efficiency of conversion. For example, as disclosed herein, certain modifications to oligonucleotides confer a greater improvement to the efficiency of conversion than other modifications.

Efficiency of conversion is defined herein as the percentage of recovered substrate molecules that have undergone a conversion event. Depending on the nature of the target genetic material, e.g. the genome of a cell, efficiency could be represented as the proportion of cells or clones containing an extrachromosomal element that exhibit a particular phenotype. Alternatively, representative samples of the target genetic material can be sequenced to determine the percentage that have acquired the desire change. The oligonucleotides of the invention in different embodiments can alter DNA one, two,
20 three, four, five, six, seven, eight, nine, ten, twelve, fifteen, twenty, thirty, and fifty or more fold more than control oligonucleotides. Such control oligonucleotides are oligonucleotides with fully phosphorothiolated linkages, oligonucleotides that are fully substituted with 2'-O-methyl analogs, a perfectly matched oligonucleotide that is fully complementary to a target sequence or a chimeric DNA-RNA double hairpin oligonucleotide such as disclosed in US Patent 5,565,350.
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In addition, for a given oligonucleotide length, additional modifications interfere with the ability of the oligonucleotide to act in concert with the cellular recombination or repair enzyme machinery which is necessary and required to mediate a targeted substitution, addition or deletion event in DNA. For
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example, fully phosphorothiolated or fully 2-O-methylated molecules are inefficient in targeted gene alteration.

The oligonucleotides of the invention as optimized for the purpose of targeted alteration of genetic material, including gene knockout or repair, are different in structure from antisense oligo-
5 nucleotides that may possess a similar mixed chemical composition backbone. The oligonucleotides of the invention differ from such antisense oligonucleotides in chemical composition, structure, sequence, and in their ability to alter genomic DNA. Significantly, antisense oligonucleotides fail to direct targeted gene alteration. The oligonucleotides of the invention may target either the Watson or the Crick strand of DNA and can include any component of the genome including, for example, intron and exon sequences.
10 The preferred embodiment of the invention is a modified oligonucleotide that binds to the non-transcribed strand of a genomic DNA duplex. In other words, the preferred oligonucleotides of the invention target the sense strand of the DNA, i.e. the oligonucleotides of the invention are complementary to the non-transcribed strand of the target duplex DNA. The sequence of the non-transcribed strand of a DNA duplex is found in the mRNA produced from that duplex, given that mRNA uses uracil-containing
15 nucleotides in place of thymine-containing nucleotides.

Moreover, the initial observation that single-stranded oligonucleotides comprising these modifications and lacking any particular triplex forming domain have reproducibly enhanced gene repair activity in a variety of assay systems as compared to a chimeric RNA-DNA double-stranded hairpin control or single-stranded oligonucleotides comprising other backbone modifications was surprising. The single-stranded molecules of the invention totally lack the complementary RNA binding structure that stabilizes a normal chimeric double-stranded hairpin of the type disclosed in U.S. Patent 5,565,350 yet is more effective in producing targeted base conversion as compared to such a chimeric RNA-DNA double-stranded hairpin. In addition, the molecules of the invention lack any particular triplex forming domain involved in Hoogsteen interactions with the DNA double helix and required by other known
20 oligonucleotides in other oligonucleotide dependant gene conversion systems. Although the lack of these functional domains was expected to decrease the efficiency of an alteration in a sequence, just the opposite occurs: the efficiency of sequence alteration using the modified oligonucleotides of the invention is higher than the efficiency of sequence alteration using a chimeric RNA-DNA hairpin targeting the same sequence alteration. Moreover, the efficiency of sequence alteration or gene conversion directed by an
25 unmodified oligonucleotide is many times lower as compared to a control chimeric RNA-DNA molecule or the modified oligonucleotides of the invention targeting the same sequence alteration. Similarly,
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molecules containing at least 3 2'-O-methyl base analogs are about four to five fold less efficient as compared to an oligonucleotide having the same number of phosphorothioate linkages.

The oligonucleotides of the present invention for alteration of a single base are about 17 to about 121 nucleotides in length, preferably about 17 to about 74 nucleotides in length. Most preferably, however, the oligonucleotides of the present invention are at least about 25 bases in length, unless there are self-dimerization structures within the oligonucleotide. If the oligonucleotide has such an unfavorable structure, lengths longer than 35 bases are preferred. Oligonucleotides with modified ends both shorter and longer than certain of the exemplified, modified oligonucleotides herein function as gene repair or gene knockout agents and are within the scope of the present invention.

Once an oligomer is chosen, it can be tested for its tendency to self-dimerize, since self-dimerization may result in reduced efficiency of alteration of genetic information. Checking for self-dimerization tendency can be accomplished manually or, more preferably, by using a software program. One such program is Oligo Analyzer 2.0, available through Integrated DNA Technologies (Coralville, IA 52241) (<http://www.idtdna.com>); this program is available for use on the world wide web at

<http://www.idtdna.com/program/oligoanalyzer/>
[oligoanalyzer.asp](http://www.idtdna.com/program/oligoanalyzer/).

For each oligonucleotide sequence input into the program, Oligo Analyzer 2.0 reports possible self-dimerized duplex forms, which are usually only partially duplexed, along with the free energy change associated with such self-dimerization. Delta G-values that are negative and large in magnitude, indicating strong self-dimerization potential, are automatically flagged by the software as "bad". Another software program that analyzes oligomers for pair dimer formation is Primer Select from DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715, Phone: (608) 258-7420 (<http://www.dnastar.com/products/PrimerSelect.html>).

If the sequence is subject to significant self-dimerization, the addition of further sequence flanking the "repair" nucleotide can improve gene correction frequency.

Generally, the oligonucleotides of the present invention are identical in sequence to one strand of the target DNA, which can be either strand of the target DNA, with the exception of one or more targeted bases positioned within the DNA domain of the oligonucleotide, and preferably toward the middle between the modified terminal regions. Preferably, the difference in sequence of the oligonucleotide as compared to the targeted genomic DNA is located at about the middle of the oligonucleotide sequence. In a preferred embodiment, the oligonucleotides of the invention are complementary to the non-transcribed strand of a duplex. In other words, the preferred oligonucleotides target the sense strand of the DNA, i.e.

the oligonucleotides of the invention are preferably complementary to the strand of the target DNA the sequence of which is found in the mRNA.

The oligonucleotides of the invention can include more than a single base change. In an oligonucleotide that is about a 70-mer, with at least one modified residue incorporated on the ends, as disclosed herein, multiple bases can be simultaneously targeted for change. The target bases may be up to 27 nucleotides apart and may not be changed together in all resultant plasmids in all cases. There is a frequency distribution such that the closer the target bases are to each other in the central DNA domain within the oligonucleotides of the invention, the higher the frequency of change in a given cell. Target bases only two nucleotides apart are changed together in every case that has been analyzed. The farther apart the two target bases are, the less frequent the simultaneous change. Thus, oligonucleotides of the invention may be used to repair or alter multiple bases rather than just one single base. For example, in a 74-mer oligonucleotide having a central base targeted for change, a base change event up to about 27 nucleotides away can also be effected. The positions of the altering bases within the oligonucleotide can be optimized using any one of the assays described herein. Preferably, the altering bases are at least about 8 nucleotides from one end of the oligonucleotide.

The oligonucleotides of the present invention can be introduced into cells by any suitable means. According to certain preferred embodiments, the modified oligonucleotides may be used alone. Suitable means, however, include the use of polycations, cationic lipids, liposomes, polyethylenimine (PEI), electroporation, biolistics, microinjection and other methods known in the art to facilitate cellular uptake. According to certain preferred embodiments of the present invention, the isolated cells are treated in culture according to the methods of the invention, to mutate or repair a target gene. Modified cells may then be reintroduced into the organism as, for example, in bone marrow having a targeted gene. Alternatively, modified cells may be used to regenerate the whole organism as, for example, in a plant having a desired targeted genomic change. In other instances, targeted genomic alteration, including repair or mutagenesis, may take place *in vivo* following direct administration of the modified, single-stranded oligonucleotides of the invention to a subject.

The single-stranded, modified oligonucleotides of the present invention have numerous applications as gene repair, gene modification, or gene knockout agents. Such oligonucleotides may be advantageously used, for example, to introduce or correct multiple point mutations. Each mutation leads to the addition, deletion or substitution of at least one base pair. The methods of the present invention offer distinct advantages over other methods of altering the genetic makeup of an organism, in that only the individually targeted bases are altered. No additional foreign DNA sequences are added to the

genetic complement of the organism. Such agents may, for example, be used to develop plants or animals with improved traits by rationally changing the sequence of selected genes in cultured cells. Modified cells are then cloned into whole plants or animals having the altered gene. See, e.g., U.S. Patent 6,046,380 and U.S. Patent 5,905,185 incorporated hererin by reference. Such plants or animals produced using the compositions of the invention lack additional undesirable selectable markers or other foreign DNA sequences. Targeted base pair substitution or frameshift mutations introduced by an oligonucleotide in the presence of a cell-free extract also provides a way to modify the sequence of extrachromosomal elements, including, for example, plasmids, cosmids and artificial chromosomes. The oligonucleotides of the invention also simplify the production of transgenic animals having particular modified or inactivated genes. Altered animal or plant model systems such as those produced using the methods and oligonucleotides of the invention are invaluable in determining the function of a gene and in evaluating drugs. The oligonucleotides and methods of the present invention may also be used for gene therapy to correct mutations causative of human diseases.

The purified oligonucleotide compositions may be formulated in accordance with routine procedures as a pharmaceutical composition adapted for bathing cells in culture, for microinjection into cells in culture, and for intravenous administration to human beings or animals. Typically, compositions for cellular administration or for intravenous administration into animals, including humans, are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anaesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients will be supplied either separately or mixed together in unit dosage form, for example, as a dry, lyophilized powder or water-free concentrate. The composition may be stored in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent in activity units. Where the composition is administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade "water for injection" or saline. Where the composition is to be administered by injection, an ampule of sterile water for injection or saline may be provided so that the ingredients may be mixed prior to administration.

Pharmaceutical compositions of this invention comprise the compounds of the present invention and pharmaceutically acceptable salts thereof, with any pharmaceutically acceptable ingredient, excipient, carrier, adjuvant or vehicle.

The oligonucleotides of the invention are preferably administered to the subject in the form of an injectable composition. The composition is preferably administered parenterally, meaning intravenously, intraarterially, intrathecally, interstitially or intracavitarilly. Pharmaceutical compositions of

this invention can be administered to mammals including humans in a manner similar to other diagnostic or therapeutic agents. The dosage to be administered, and the mode of administration will depend on a variety of factors including age, weight, sex, condition of the subject and genetic factors, and will ultimately be decided by medical personnel subsequent to experimental determinations of varying dosage
5 as described herein. In general, dosage required for correction and therapeutic efficacy will range from about 0.001 to 50,000 µg/kg, preferably between 1 to 250 µg/kg of host cell or body mass, and most preferably at a concentration of between 30 and 60 micromolar.

For cell administration, direct injection into the nucleus, biolistic bombardment, electroporation, liposome transfer and calcium phosphate precipitation may be used. In yeast, lithium acetate or spheroplast transformation may also be used. In a preferred method, the administration is performed with a liposomal transfer compound, e.g., DOTAP (Boehringer-Mannheim) or an equivalent such as lipofectin. The amount of the oligonucleotide used is about 500 nanograms in 3 micrograms of DOTAP per 100,000 cells. For electroporation, between 20 and 2000 nanograms of oligonucleotide per million cells to be electroporated is an appropriate range of dosages which can be increased to improve efficiency of genetic alteration upon review of the appropriate sequence according to the methods described herein.
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Another aspect of the invention is a kit comprising at least one oligonucleotide of the invention. The kit may comprise an addition reagent or article of manufacture. The additional reagent or article of manufacture may comprise a cell extract, a cell, or a plasmid, such as one of those disclosed in the Figures herein, for use in an assay of the invention.
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Brief Description Of The Drawings

Figure 1. *Flow diagram for the generation of modified single-stranded oligonucleotides.*

The upper strands of chimeric oligonucleotides I and II are separated into pathways resulting in the generation of single-stranded oligonucleotides that contain (A) 2'-O-methyl RNA nucleotides or (B) phosphorothioate linkages. Fold changes in repair activity for correction of kan^s in the HUH7 cell-free extract are presented in parenthesis. HUH7 cells are described in Nakabayashi et al., Cancer Research 42: 3858-3863 (1982). Each single-stranded oligonucleotide is 25 bases in length and contains a G residue mismatched to the complementary sequence of the kan^s gene. The numbers 3, 6, 8, 10, 12 and 12.5 respectively indicate how many phosphorothioate linkages (S) or 2'-O-methyl RNA nucleotides (R)
25 are at each end of the molecule. Hence oligo 12S/25G contains an all phosphorothioate backbone, displayed as a dotted line. Smooth lines indicate DNA residues, wavy lines indicate 2'-O-methyl RNA
30

residues and the carat indicates the mismatched base site (G). Figure 1(C) provides a schematic plasmid indicating the sequence of the kan chimeric double-stranded hairpin oligonucleotide (left) and the sequence the tet chimeric double-stranded hairpin oligonucleotide used in other experiments. Figure 1(D) provides a flow chart of a kan experiment in which a chimeric double-stranded hairpin oligonucleotide is used.

Figure 2. *Genetic readout system for correction of a point mutation in plasmid pK^sm4021.* A mutant kanamycin gene harbored in plasmid pK^sm4021 is the target for correction by oligonucleotides. The mutant G is converted to a C by the action of the oligo. Corrected plasmids confer resistance to kanamycin in *E.coli* (DH10B) after electroporation leading to the genetic readout and colony counts.

Figure 3: *Target plasmid and sequence correction of a frameshift mutation by chimeric and single-stranded oligonucleotides.* (A) Plasmid pT^sΔ208 contains a single base deletion mutation at position 208 rendering it unable to confer tet resistance. The target sequence presented below indicates the insertion of a T directed by the oligonucleotides to re-establish the resistant phenotype. (B) DNA sequence confirming base insertion directed by Tet 3S/25G; the yellow highlight indicates the position of frameshift repair.

Figure 4. *DNA sequences of representative kan^r colonies.* Confirmation of sequence alteration directed by the indicated molecule is presented along with a table outlining codon distribution. Note that 10S/25G and 12S/25G elicit both mixed and unfaithful gene repair. The number of clones sequenced is listed in parentheses next to the designation for the single-stranded oligonucleotide. A plus (+) symbol indicates the codon identified while a figure after the (+) symbol indicates the number of colonies with a particular sequence. TAC/TAG indicates a mixed peak. Representative DNA sequences are presented below the table with yellow highlighting altered residues.

Figure 5. *Gene correction in HeLa cells.* Representative oligonucleotides of the invention are co-transfected with the pCMVneo(')FlAsH plasmid (shown in Figure 9) into HeLa cells. Ligand is diffused into cells after co-transfection of plasmid and oligonucleotides. Green fluorescence indicates gene correction of the mutation in the antibiotic resistance gene. Correction of the mutation results in the expression of a fusion protein that carries a marker ligand binding site and when the fusion protein binds the ligand, a green fluorescence is emitted. The ligand is produced by Aurora Biosciences and can readily diffuse into cells enabling a measurement of corrected protein function; the protein must bind the ligand directly to induce fluorescence. Hence cells bearing the corrected plasmid gene appear green while "uncorrected" cells remain colorless.

Figure 6. Z-series imaging of corrected cells. Serial cross-sections of the HeLa cell represented in Figure 5 are produced by Zeiss 510 LSM confocal microscope revealing that the fusion protein is contained within the cell.

Figure 7. Hygromycin-eGFP target plasmids. (A) Plasmid pAURHYG(ins)GFP contains a single base insertion mutation between nucleotides 136 and 137, at codon 46, of the Hygromycin B coding sequence (cds) which is transcribed from the constitutive ADH1 promoter. The target sequence presented below indicates the deletion of an A and the substitution of a C for a T directed by the oligonucleotides to re-establish the resistant phenotype. (B) Plasmid pAURHYG(rep)GFP contains a base substitution mutation introducing a G at nucleotide 137, at codon 46, of the Hygromycin B coding sequence (cds). The target sequence presented below the diagram indicates the amino acid conservative replacement of G with C, restoring gene function.

Figure 8. Oligonucleotides for correction of hygromycin resistance gene. The sequence of the oligonucleotides used in experiments to assay correction of a hygromycin resistance gene are shown. DNA residues are shown in capital letters, RNA residues are shown in lowercase and nucleotides with a phosphorothioate backbone are capitalized and underlined.

Figure 9. pAURNeo(-)FIAsH plasmid. This figure describes the plasmid structure, target sequence, oligonucleotides, and the basis for detection of the gene alteration event by fluorescence.

Figure 10. pYESHyg(x)eGFP plasmid. This plasmid is a construct similar to the pAURHyg(x)eGFP construct shown in Figure 7, except the promoter is the inducible GAL1 promoter. This promoter is inducible with galactose, leaky in the presence of raffinose, and repressed in the presence of dextrose.

The following examples are provided by way of illustration only, and are not intended to limit the scope of the invention disclosed herein.

EXAMPLE 1
Assay Method For Base Alteration
And Preferred Oligonucleotide Selection

In this example, single-stranded and double-hairpin oligonucleotides with chimeric backbones (see Figure 1 for structures (A and B) and sequences (C and D) of assay oligonucleotides) are used to correct a point mutation in the kanamycin gene of pK^sm4021 (Figure 2) or the tetracycline gene of pT^sΔ208 (Figure 3). All kan oligonucleotides share the same 25 base sequence surrounding the target base identified for change, just as all tet oligonucleotides do. The sequence is given in Figures 1C and Figure 1D. Each plasmid contains a functional ampicillin gene. Kanamycin gene function is restored

when a G at position 4021 is converted to a C (via a substitution mutation); tetracycline gene function is restored when a deletion at position 208 is replaced by a C (via frameshift mutation). A separate plasmid, pAURNeo(-)FIAsH (Figure 9), bearing the kan^s gene is used in the cell culture experiments. This plasmid was constructed by inserting a synthetic expression cassette containing a neomycin phosphotransferase (kanamycin resistance) gene and an extended reading frame that encodes a receptor for the FIAsH ligand into the pAUR123 shuttle vector (Panvera Corp., Madison, WI). The resulting construct replicates in *S. cerevisiae* at low copy number, confers resistance to aureobasidinA and constitutively expresses either the Neo+/FIAsH fusion product (after alteration) or the truncated Neo-/FIAsH product (before alteration) from the ADH1 promoter. By extending the reading frame of this gene to code for a unique peptide sequence capable of binding a small ligand to form a fluorescent complex, restoration of expression by correction of the stop codon can be detected in real time using confocal microscopy.

Additional constructs can be made to test additional gene alteration events.

We also construct three mammalian expression vectors, pHyg(rep)eGFP, pHyg(Δ)eGFP, pHyg(ins)eGFP, that contain a substitution mutation at nucleotide 137 of the hygromycin-B coding sequence. (rep) indicates a T137→G replacement, (Δ) represents a deletion of the G137 and (ins) represents an A insertion between nucleotides 136 and 137. All point mutations create a nonsense termination codon at residue 46. We use pHygEGFP plasmid (Invitrogen, CA) DNA as a template to introduce the mutations into the hygromycin-eGFP fusion gene by a two step site-directed mutagenesis PCR protocol. First, we generate overlapping 5' and a 3' amplicons surrounding the mutation site by PCR for each of the point mutation sites. A 215 bp 5' amplicon for the (rep), (Δ) or (ins) was generated by polymerization from oligonucleotide primer HygEGFPf (5'-AATACGACTCACTATAGG-3') to primer Hygrepr (5'GACCTATCCACGCCCTCC-3'), HygΔr (5'-GACTATCCACGCCCTCC-3'), or Hyginsr (5'-GACATTATCCACGCCCTCC-3'), respectively. We generate a 300bp 3' amplicon for the (rep), (Δ) or (ins) by polymerization from oligonucleotide primers Hygrefp (5'-CTGGGATAGGTCTGCGG-3'), HygΔf (5'-CGTGGATAGTCCTGCGG-3'), Hyginsf (5'-CGTGGATAATGTCCTGCGG-3'), respectively to primer HygEGFPr (5'-AAATCACGCCATGTAGTG-3'). We mix 20 ng of each of the resultant 5' and 3' overlapping amplicon mutation sets and use the mixture as a template to amplify a 523 bp fragment of the Hygromycin gene spanning the KpnI and RsrII restriction endonuclease sites. We use the Expand PCR system (Roche) to generate all amplicons with 25 cycles of denaturing at 94°C for 10 seconds, annealing at 55°C for 20 seconds and elongation at 68°C for 1 minute. We digest 10 µg of vector pHygEGFP and 5 µg of the resulting fragments for each mutation with KpnI and RsrII (NEB) and gel purify the fragment for enzymatic ligation. We ligate each mutated insert into pHygEGFP vector at 3:1 molar ration using T4

DNA ligase (Roche). We screen clones by restriction digest, confirm the mutation by Sanger dideoxy chain termination sequencing and purify the plasmid using a Qiagen maxiprep kit.

Oligonucleotide synthesis and cells. Chimeric oligonucleotides and single-stranded oligonucleotides (including those with the indicated modifications) are synthesized using available phosphoramidites on controlled pore glass supports. After deprotection and detachment from the solid support, each oligonucleotide is gel-purified using, for example, procedures such as those described in Gamper et al., *Biochem.* 39, 5808-5816 (2000) and the concentrations determined spectrophotometrically (33 or 40 µg/ml per A₂₆₀ unit of single-stranded or hairpin oligomer). HUH7 cells are grown in DMEM, 10% FBS, 2mM glutamine, 0.5% pen/strep. The *E.coli* strain, DH10B, is obtained from Life Technologies (Gaithersburg, MD); DH10B cells contain a mutation in the RECA gene (*recA*).

Cell-free extracts. We prepare cell-free extracts from HUH7 cells or other mammalian cells, as follows. We employ this protocol with essentially any mammalian cell including, for example, H1299 cells (human epithelial carcinoma, non-small cell lung cancer), C127I (immortal murine mammary epithelial cells), MEF (mouse embryonic fibroblasts), HEC-1-A (human uterine carcinoma), HCT15 (human colon cancer), HCT116 (human colon carcinoma), LoVo (human colon adenocarcinoma), and HeLa (human cervical carcinoma). We harvest approximately 2x10⁸ cells. We then wash the cells immediately in cold hypotonic buffer (20 mM HEPES, pH7.5; 5 mM KCl; 1.5 mM MgCl₂; 1 mM DTT) with 250 mM sucrose. We then resuspend the cells in cold hypotonic buffer without sucrose and after 15 minutes we lyse the cells with 25 strokes of a Dounce homogenizer using a tight fitting pestle. We incubate the lysed cells for 60 minutes on ice and centrifuge the sample for 15 minutes at 12000xg. The cytoplasmic fraction is enriched with nuclear proteins due to the extended co-incubation of the fractions following cell breakage. We then immediately aliquote and freeze the supernatant at -80°C. We determine the protein concentration in the extract by the Bradford assay.

We also perform these experiments with cell-free extracts obtained from fungal cells, including, for example, *S. cerevisiae* (yeast), *Ustilago maydis*, and *Candida albicans*. For example, we grow yeast cells into log phase in 2L YPD medium for 3 days at 30°C. We then centrifuge the cultures at 5000xg, resuspend the pellets in a 10% sucrose, 50 mM Tris, 1mM EDTA lysis solution and freeze them on dry ice. After thawing, we add KCl, spermidine and lyticase to final concentrations of 0.25 mM, 5 mM and 0.1 mg/ml, respectively. We incubate the suspension on ice for 60 minutes, add PMSF and Triton X100 to final concentrations of 0.1 mM and 0.1% and continue to incubate on ice for 20 minutes. We centrifuge the lysate at 3000xg for 10 minutes to remove larger debris. We then remove the supernatant and clarify it by centrifuging at 30000xg for 15 minutes. We then add glycerol to the clarified extract to a

concentration of 10% (v/v) and freeze aliquots at -80°C. We determine the protein concentration of the extract by the Bradford assay.

Reaction mixtures of 50 µl are used, consisting of 10-30 µg protein of cell-free extract, which can be optionally substituted with purified proteins or enriched fractions, about 1.5 µg chimeric double-hairpin oligonucleotide or 0.55 µg single-stranded molecule (3S/25G or 6S/25G, see Figure 1), and 1 µg of plasmid DNA (see Figures 2 and 3) in a reaction buffer of 20 mM Tris, pH 7.4, 15 mM MgCl₂, 0.4 mM DTT, and 1.0 mM ATP. Reactions are initiated with extract and incubated at 30°C for 45 min. The reaction is stopped by placing the tubes on ice and then immediately deproteinized by two phenol/chloroform (1:1) extractions. Samples are then ethanol precipitated. The nucleic acid is pelleted at 15,000 r.p.m. at 4°C for 30 min., is washed with 70% ethanol, resuspended in 50 µl H₂O, and is stored at -20°C. 5 µl of plasmid from the resuspension (~100 ng) was transfected in 20 µl of DH10B cells by electroporation (400 V, 300 µF, 4 kΩ) in a Cell-Porator apparatus (Life Technologies). After electroporation, cells are transferred to a 14 ml Falcon snap-cap tube with 2 ml SOC and shaken at 37°C for 1 h. Enhancement of final kan colony counts is achieved by then adding 3 ml SOC with 10 µg/ml kanamycin and the cell suspension is shaken for a further 2 h at 37°C. Cells are then spun down at 3750 x g and the pellet is resuspended in 500 µl SOC. 200 µl is added undiluted to each of two kanamycin (50 µg/ml) agar plates and 200 µl of a 10⁵ dilution is added to an ampicillin (100 µg/ml) plate. After overnight 37°C incubation, bacterial colonies are counted using an AccuCount 1000 (Biologics). Gene conversion effectiveness is measured as the ratio of the average of the kan colonies on both plates per amp colonies multiplied by 10⁻⁵ to correct for the amp dilution.

The following procedure can also be used. 5 µl of resuspended reaction mixtures (total volume 50 µl) are used to transform 20 µl aliquots of electro-competent ΔH10B bacteria using a Cell-Porator apparatus (Life Technologies). The mixtures are allowed to recover in 1 ml SOC at 37°C for 1 hour at which time 50 µg/ml kanamycin or 12 µg/ml tetracycline is added for an additional 3 hours. Prior to plating, the bacteria are pelleted and resuspended in 200 µl of SOC. 100 µl aliquots are plated onto kan or tet agar plates and 100 µl of a 10⁻⁴ dilution of the cultures are concurrently plated on agar plates containing 100 µg/ml of ampicillin. Plating is performed in triplicate using sterile Pyrex beads. Colony counts are determined by an Accu-count 1000 plate reader (Biologics). Each plate contains 200-500 ampicillin resistant colonies or 0-500 tetracycline or kanamycin resistant colonies. Resistant colonies are selected for plasmid extraction and DNA sequencing using an ABI Prism kit on an ABI 310 capillary sequencer (PE Biosystems).

Chimeric single-stranded oligonucleotides. In Figure 1 the upper strands of chimeric oligonucleotides I and II are separated into pathways resulting in the generation of single-stranded oligonucleotides that contain (Figure 1A) 2'-O-methyl RNA nucleotides or (Figure 1B) phosphorothioate linkages. Fold changes in repair activity for correction of kan^s in the HUH7 cell-free extract are presented in parenthesis. Each single-stranded oligonucleotide is 25 bases in length and contains a G residue mismatched to the complementary sequence of the kan^s gene.

Molecules bearing 3, 6, 8, 10 and 12 phosphorothioate linkages in the terminal regions at each end of a backbone with a total of 24 linkages (25 bases) are tested in the kan^s system. Alternatively, molecules bearing 2, 4, 5, 7, 9 and 11 in the terminal regions at each end are tested. The results of one such experiment, presented in Table 1 and Figure 1B, illustrate an enhancement of correction activity directed by some of these modified structures. In this illustrative example, the most efficient molecules contained 3 or 6 phosphorothioate linkages at each end of the 25-mer; the activities are approximately equal (molecules IX and X with results of 3.09 and 3.7 respectively). A reduction in alteration activity may be observed as the number of modified linkages in the molecule is further increased. Interestingly, a single-strand molecule containing 24 phosphorothioate linkages is minimally active suggesting that this backbone modification when used throughout the molecule supports only a low level of targeted gene repair or alteration. Such a non-altering, completely modified molecule can provide a baseline control for determining efficiency of correction for a specific oligonucleotide molecule of known sequence in defining the optimum oligonucleotide for a particular alteration event.

The efficiency of gene repair directed by phosphorothioate-modified, single-stranded molecules, in a length dependent fashion, led us to examine the length of the RNA modification used in the original chimera as it relates to correction. Construct III represents the "RNA-containing" strand of chimera I and, as shown in Table 1 and Figure 2A, it promotes inefficient gene repair. But, as shown in the same figure, reducing the RNA residues on each end from 10 to 3 increases the frequency of repair. At equal levels of modification, however, 25-mers with 2'-O-methyl ribonucleotides were less effective gene repair agents than the same oligomers with phosphorothioate linkages. These results reinforce the fact that an RNA containing oligonucleotide is not as effective in promoting gene repair or alteration as a modified DNA oligonucleotide.

Repair of the kanamycin mutation requires a G→C exchange. To confirm that the specific desired correction alteration was obtained, colonies selected at random from multiple experiments are processed and the isolated plasmid DNA is sequenced. As seen in Figure 4, colonies generated through the action of the single-stranded molecules 3S/25G (IX), 6S/25G (X) and 8S/25G (XI) respectively

contained plasmid molecules harboring the targeted base correction. While a few colonies appeared on plates derived from reaction mixtures containing 25-mers with 10 or 12 thioate linkages on both ends, the sequences of the plasmid molecules from these colonies contain nonspecific base changes. In these illustrative examples, the second base of the codon is changed (see Figure 3). These results show that 5 modified single-strands can direct gene repair, but that efficiency and specificity are reduced when the 25-mers contain 10 or more phosphorothioate linkages at each end.

In Figure 1, the numbers 3, 6, 8, 10, 12 and 12.5 respectively indicate how many phosphorothioate linkages (S) or 2'-O-methyl RNA nucleotides (R) are at each end of the exemplified molecule although other molecules with 2, 4, 5, 7, 9 and 11 modifications at each end can also be tested. 10 Hence oligo 12S/25G represents a 25-mer oligonucleotide which contains 12 phosphorothioate linkages on each side of the central G target mismatch base producing a fully phosphorothioate linked backbone, displayed as a dotted line. The dots are merely representative of a linkage in the figure and do not depict the actual number of linkages of the oligonucleotide. Smooth lines indicate DNA residues, wavy lines indicate 2'-O-methyl RNA residues and the carat indicates the mismatched base site (G).

15 *Correction of a mutant kanamycin gene in cultured mammalian cells.* The experiments are performed using different mammalian cells, including, for example, 293 cells (transformed human primary kidney cells), HeLa cells (human cervical carcinoma), and H1299 (human epithelial carcinoma, non-small cell lung cancer). HeLa cells are grown at 37°C and 5% CO₂ in a humidified incubator to a density of 2 x 10⁵ cells/ml in an 8 chamber slide (Lab-Tek). After replacing the regular DMEM with Optimem, the cells are co-transfected with 10 µg of plasmid pAURNeo(-)FIAsH and 5 µg of modified 20 single-stranded oligonucleotide (3S/25G) that is previously complexed with 10 µg lipofectamine, according to the manufacturer's directions (Life Technologies). The cells are treated with the liposome-DNA-oligo mix for 6 hrs at 37°C. Treated cells are washed with PBS and fresh DMEM is added. After a 16-18 hr recovery period, the culture is assayed for gene repair. The same oligonucleotide used in the 25 cell-free extract experiments is used to target transfected plasmid bearing the kan^s gene. Correction of the point mutation in this gene eliminates a stop codon and restores full expression. This expression can be detected by adding a small non-fluorescent ligand that bound to a C-C-R-E-C-C sequence in the genetically modified carboxy terminus of the kan protein, to produce a highly fluorescent complex (FIAsH system, Aurora Biosciences Corporation). Following a 60 min incubation at room temperature with the 30 ligand (FIAsH-EDT2), cells expressing full length kan product acquire an intense green fluorescence detectable by fluorescence microscopy using a fluorescein filter set. Similar experiments are performed using the HygeGFP target as described in Example 2 with a variety of mammalian cells, including, for

example, COS-1 and COS-7 cells (African green monkey), and CHO-K1 cells (Chinese hamster ovary). The experiments are also performed with PG12 cells (rat pheochromocytoma) and ES cells (human embryonic stem cells).

Summary of experimental results. Tables 1, 2 and 3 respectively provide data on the efficiency of gene repair directed by single-stranded oligonucleotides. Table 1 presents data using a cell-free extract from human liver cells (HUH7) to catalyze repair of the point mutation in plasmid pkan^sm4021 (see Figure 1). Table 2 illustrates that the oligomers are not dependent on MSH2 or MSH3 for optimal gene repair activity. Table 3 illustrates data from the repair of a frameshift mutation (Figure 3) in the tet gene contained in plasmid pTetΔ208. Table 4 illustrates data from repair of the pkan^sm4021 point mutation catalyzed by plant cell extracts prepared from canola and musa (banana). Colony numbers are presented as kan^r or tet^r and fold increases (single strand versus double hairpin) are presented for kan^r in Table 1.

Figure 5A is a confocal picture of HeLa cells expressing the corrected fusion protein from an episomal target. Gene repair is accomplished by the action of a modified single-stranded oligonucleotide containing 3 phosphorothioate linkages at each end (3S/25G). Figure 5B represents a "Z-series" of HeLa cells bearing the corrected fusion gene. This series sections the cells from bottom to top and illustrates that the fluorescent signal is "inside the cells".

Results. In summary, we have designed a novel class of single-stranded oligonucleotides with backbone modifications at the termini and demonstrate gene repair/conversion activity in mammalian and plant cell-free extracts. We confirm that the all DNA strand of the RNA-DNA double-stranded double hairpin chimera is the active component in the process of gene repair. In some cases, the relative frequency of repair by the novel oligonucleotides of the invention is elevated approximately 3-4-fold when compared to frequencies directed by chimeric RNA-DNA double hairpin oligonucleotides.

This strategy centers around the use of extracts from various sources to correct a mutation in a plasmid using a modified single-stranded or a chimeric RNA-DNA double hairpin oligonucleotide. A mutation is placed inside the coding region of a gene conferring antibiotic resistance in bacteria, here kanamycin or tetracycline. The appearance of resistance is measured by genetic readout in *E.coli* grown in the presence of the specified antibiotic. The importance of this system is that both phenotypic alteration and genetic inheritance can be measured. Plasmid pK^sm4021 contains a mutation (T-G) at residue 4021 rendering it unable to confer antibiotic resistance in *E.coli*. This point mutation is targeted for repair by oligonucleotides designed to restore kanamycin resistance. To avoid concerns of

plasmid contamination skewing the colony counts, the directed correction is from G→C rather than G→T (wild-type). After isolation, the plasmid is electroporated into the DH10B strain of *E.coli*, which contains inactive RecA protein. The number of kanamycin colonies is counted and normalized by ascertaining the number of ampicillin colonies, a process that controls for the influence of electroporation. The number of colonies generated from three to five independent reactions was averaged and is presented for each experiment. A fold increase number is recorded to aid in comparison.

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The original RNA-DNA double hairpin chimera design, e.g., as disclosed in U.S.

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Patent 5,565,350, consists of two hybridized regions of a single-stranded oligonucleotide folded into a double hairpin configuration. The double-stranded targeting region is made up of a 5 base pair DNA/DNA segment bracketed by 10 base pair RNA/DNA segments. The central base pair is mismatched to the corresponding base pair in the target gene. When a molecule of this design is used to correct the kan^s mutation, gene repair is observed (I in Figure 1A). Chimera II (Figure 1B) differs partly from chimera I in that only the DNA strand of the double hairpin is mismatched to the target sequence. When this chimera was used to correct the kan^s mutation, it was twice as active. In the same study, repair function could be further increased by making the targeting region of the chimera a continuous RNA/DNA hybrid.

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Frame shift mutations are repaired. By using plasmid pT^sΔ208, described in Figure 1(C) and Figure 3, the capacity of the modified single-stranded molecules that showed activity in correcting a point mutation, can be tested for repair of a frameshift. To determine efficiency of correction of the mutation, a chimeric oligonucleotide (Tet I), which is designed to insert a T residue at position 208, is used. A modified single-stranded oligonucleotide (Tet IX) directs the insertion of a T residue at this same site. Figure 3 illustrates the plasmid and target bases designated for change in the experiments. When all reaction components are present (extract, plasmid, oligomer), tetracycline resistant colonies appear. The colony count increases with the amount of oligonucleotide used up to a point beyond which the count falls off (Table 3). No colonies above background are observed in the absence of either extract or oligonucleotide, nor when a modified single-stranded molecule bearing perfect complementarity is used. Figure 3 represents the sequence surrounding the target site and shows that a T residue is inserted at the correct site. We have isolated plasmids from fifteen colonies obtained in three independent experiments and each analyzed sequence revealed the same precise nucleotide insertion. These data suggest that the single-stranded molecules used initially for point mutation correction can also repair nucleotide deletions.

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Comparison of phosphorothioate oligonucleotides to 2'-O-methyl substituted oligonucleotides. From a comparison of molecules VII and XI, it is apparent that gene repair is more

subject to inhibition by RNA residues than by phosphorothioate linkages. Thus, even though both of these oligonucleotides contain an equal number of modifications to impart nuclease resistance, XI (with 16 phosphorothioate linkages) has good gene repair activity while VII (with 16 2'-O-methyl RNA residues) is inactive. Hence, the original chimeric double hairpin oligonucleotide enabled correction directed, in large part, by the strand containing a large region of contiguous DNA residues.

Oligonucleotides can target multiple nucleotide alterations within the same template. The ability of individual single-stranded oligonucleotides to correct multiple mutations in a single target template is tested using the plasmid pK^sm4021 and the following single-stranded oligonucleotides modified with 3 phosphorothioate linkages at each end (indicated as underlined nucleotides): Oligo1 is a 25-mer with the sequence ITCGATAAGCCTATGCTGACCCGTG corrects the original mutation present in the kanamycin resistance gene of pK^sm4021 as well as directing another alteration 2 basepairs away in the target sequence (both indicated in boldface); Oligo2 is a 70-mer with the 5'-end sequence TCGGCTACGACTGGGCACAAACAGACAATTGGC with the remaining nucleotides being completely complementary to the kanamycin resistance gene and also ending in 3 phosphorothioate linkages at the 3' end. Oligo2 directs correction of the mutation in pK^sm4021 as well as directing another alteration 21 basepairs away in the target sequence (both indicated in boldface).

We also use additional oligonucleotides to assay the ability of individual oligonucleotides to correct multiple mutations in the pK^sM4021 plasmid. These include, for example, a second 25-mer that alters two nucleotides that are three nucleotides apart with the sequence 5'-
TTGTGCCCAGTCTATCCGAATAGC-3'; a 70-mer that alters two nucleotides that are 21 nucleotides apart with the sequence 5'-CATCAGAGCAGCCAATTGTCTGTTGCCAGTCGTAGCCGAA
TAGCCTCTCCACCCAAAGCGGCCGGAGA-3'; and another 70-mer that alters two nucleotides that are 21 nucleotides apart with the sequence 5'-
GCTGACAGCCGGAACACGGCGGCATCAGAGCAGCCAATTGTCTGTTGCCAGTCGTAGCCGAA
AGCCT-3'. The nucleotides in the oligonucleotides that direct alteration of the target sequence are underlined and in boldface. These oligonucleotides are modified in the same way as the other oligonucleotides of the invention.

We assay correction of the original mutation in pK^sm4021 by monitoring kanamycin resistance (the second alterations which are directed by Oligo2 and Oligo3 are silent with respect to the kanamycin resistance phenotype). In addition, in experiments with Oligo2, we also monitor cleavage of the resulting plasmids using the restriction enzyme Tsp509I which cuts at a specific site present only when the second alteration has occurred (at ATT in Oligo2). We then sequence these clones to

determine whether the additional, silent alteration has also been introduced. The results of an analysis are presented below:

	Oligo1 (25-mer)	Oligo2 (70-mer)
Clones with both sites changed	9	7
Clones with a single site changed	0	2
Clones that were not changed	4	1

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Nuclease sensitivity of unmodified DNA oligonucleotide. Electrophoretic analysis of nucleic acid recovered from the cell-free extract reactions conducted here confirm that the unmodified single-stranded 25-mer did not survive incubation whereas greater than 90% of the terminally modified oligos did survive (as judged by photo-image analyses of agarose gels).

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Plant extracts direct repair. The modified single-stranded constructs can be tested in plant cell extracts. We have observed gene alteration using extracts from multiple plant sources, including, for example, Arabidopsis, tobacco, banana, maize, soybean, canola, wheat, spinach as well as spinach chloroplast extract. We prepare the extracts by grinding plant tissue or cultured cells under liquid nitrogen with a mortar and pestle. We extract 3 ml of the ground plant tissue with 1.5 ml of extraction buffer (20 mM HEPES, pH7.5; 5 mM Kcl; 1.5 mM MgCl₂; 10 mM DTT; 10% [v/v] glycerol; and 1 % [w/v] PVP). We then homogenize the samples with 15 strokes of a Dounce homogenizer. Following homogenization, we incubate the samples on ice for 1 hour and centrifuge at 3000xg for 5 minutes to remove plant cell debris. We then determine the protein concentration in the supernatants (extracts) by Bradford assay. We dispense 100 µg (protein) aliquots of the extracts which we freeze in a dry ice-ethanol bath and store at -80°C.

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We describe experiments using two sources here: a dicot (canola) and a monocot (banana, *Musa acuminata* cv. Rasthalij). Each vector directs gene repair of the kanamycin mutation (Table 4); however, the level of correction is elevated 2-3 fold relative to the frequency observed with the chimeric oligonucleotide. These results are similar to those observed in the mammalian system wherein a significant improvement in gene repair occurred when modified single-stranded molecules were used.

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Tables are attached hereto.

Table I

Gene repair activity is directed by single-stranded oligonucleotides.

Oligonucleotide	Plasmid	Extract (ug)	kan ^r colonies	Fold increase
I	pK ^S m4021	10	300	
I		20	418	1.0x
II		10	537	
II		20	748	1.78x
III		10	3	
III		20	5	0.01x
IV		10	112	
IV		20	96	0.22x
V		10	217	
V		20	342	0.81x
VI		10	6	
VI		20	39	0.093x
VII		10	0	
VII		20	0	0x
VIII		10	3	
VIII		20	5	0.01x
IX		10	936	
IX		20	1295	3.09x
X		10	1140	
X		20	1588	3.7x
XI		10	480	
XI		20	681	1.6x
XII		10	18	
XII		20	25	0.059x
XIII		10	0	
XIII		20	4	0.009x
-		20	0	
I		-	0	

Plasmid pK^Sm4021 (1 μ g), the indicated oligonucleotide (1.5 μ g chimeric oligonucleotide or 0.55 μ g single-stranded oligonucleotide; molar ratio of oligo to plasmid of 360 to 1) and either 10 or 20 μ g of HUH7 cell-free extract were incubated 45 min at 37°C. Isolated plasmid DNA was electroporated into *E. coli* (strain DH10B) and the number of kan^r colonies counted. The data represent the number of kanamycin resistant colonies per 10⁶ ampicillin resistant colonies generated from the same reaction and is the average of three

experiments (standard deviation usually less than +/- 15%). Fold increase is defined relative to 418 kan^r colonies (second reaction) and in all reactions was calculated using the 20 μ g sample.

Table II

Modified single-stranded oligomers are not dependent on MSH2 or MSH3 for optimal gene repair activity.

A. Oligonucleotide	Plasmid	Extract	kan ^r colonies
IX (3S/25G)		HUH7	637
X (6S/25G)		HUH7	836
IX		MEF2 ^{-/-}	781
X		MEF2 ^{-/-}	676
IX		MEF3 ^{-/-}	582
X		MEF3 ^{-/-}	530
IX		MEF ^{+/+}	332
X		MEF ^{+/+}	497
-		MEF2 ^{-/-}	10
-		MEF3 ^{-/-}	5
-		MEF ^{+/+}	14

Chimeric oligonucleotide (1.5 µg) or modified single-stranded oligonucleotide (0.55 µg) was incubated with 1µg of plasmid pK^sm4021 and 20µg of the indicated extracts. MEF represents mouse embryonic fibroblasts with either MSH2 (2^{-/-}) or MSH3 (3^{-/-}) deleted. MEF^{+/+} indicates wild-type mouse embryonic fibroblasts. The other reaction components were then added and processed through the bacterial readout system. The data represent the number of kanamycin resistant colonies per 10⁶ ampicillin resistant colonies.

Table III

Frameshift mutation repair is directed by single-stranded oligonucleotides

Oligonucleotide	Plasmid	Extract	tet ^r colonies
Tet IX (3S/25A; 0.5 µg)	pT ^s Δ208 (1µg)	-	0
-		20µg	0
Tet IX (0.5 µg)			48
Tet IX (1.5 µg)			130
Tet IX (2.0 µg)			68
Tet I (chimera; 1.5 µg)			48

Each reaction mixture contained the indicated amounts of plasmid and oligonucleotide.

The extract used for these experiments came from HUH7 cells. The data represent the number of tetracycline resistant colonies per 10⁶ ampicillin resistant colonies generated from the same reaction and is the average of 3 independent experiments. Tet I is a chimeric oligonucleotide and Tet IX is a modified single-stranded oligonucleotide that are designed to insert a T residue at position 208 of pT^sΔ208. These oligonucleotides are equivalent to structures I and IX in Figure 2.

Table IV

Plant cell-free extracts support gene repair by single-stranded oligonucleotides

Oligonucleotide	Plasmid	Extract	kan ^r colonies
II (chimera)	pK ^S m4021	30µg Canola	337
IX (3S/25G)		Canola	763
X (6S/25G)		Canola	882
II		<i>Musa</i>	203
IX		<i>Musa</i>	343
X		<i>Musa</i>	746
-		Canola	0
-		<i>Musa</i>	0
IX		- Canola	0
X		- <i>Musa</i>	0

Canola or Musa cell-free extracts were tested for gene repair activity on the kanamycin-sensitive gene as previously described in (18). Chimeric oligonucleotide II (1.5 µg) and modified single-stranded oligonucleotides IX and X (0.55µg) were used to correct pK^Sm4021. Total number of kan^r colonies are present per 10⁷ ampicillin resistant colonies and represent an average of four independent experiments.

Table V
*Gene repair activity in cell-free extracts prepared from yeast (*Saccharomyces cerevisiae*)*

Cell-type	Plasmid	Chimeric Oligo	SS Oligo	kan' /amp' x 10 ⁶
Wild type	pKan'm4021	1 μ g		0.36
Wild type		1 μ g	1 μ g	0.81
ΔRAD52			1 μ g	10.72
ΔRAD52				17.41
ΔPMS1		1 μ g	1 μ g	2.02
ΔPMS1				3.23

In this experiment, the kan' gene in pKan'm4021 is corrected by either a chimeric double-hairpin oligonucleotide or a single-stranded oligonucleotide containing three thioate linkages at each end (3S/25G).

EXAMPLE 2
**Yeast Cell Targeting Assay Method for Base
Alteration and Preferred Oligonucleotide Selection**

In this example, single-stranded oligonucleotides with modified backbones and double-hairpin oligonucleotides with chimeric, RNA-DNA backbones are used to measure gene repair using two episomal targets with a fusion between a hygromycin resistance gene and eGFP as a target for gene repair. These plasmids are pAURHYG(rep)GFP, which contains a point mutation in the hygromycin resistance gene (Figure 7), pAURHYG(ins)GFP, which contains a single-base insertion in the hygromycin resistance gene (Figure 7) and pAURHYG(Δ)GFP which has a single base deletion. We also use the plasmid containing a wild-type copy of the hygromycin-eGFP fusion gene, designated pAURHYG(wt)GFP, as a control. These plasmids also contain an aureobasidinA resistance gene. In pAURHYG(rep)GFP, hygromycin resistance gene function and green fluorescence from the eGFP protein are restored when a G at position 137, at codon 46 of the hygromycin B coding sequence, is converted to a C thus removing a premature stop codon in the hygromycin resistance gene coding region. In pAURHYG(ins)GFP, hygromycin resistance gene function and green fluorescence from the eGFP protein are restored when an A inserted between nucleotide positions 136 and 137, at codon 46 of the hygromycin B coding sequence, is deleted and a C is substituted for the T at position 137, thus correcting a frameshift mutation and restoring the reading frame of the hygromycin-eGFP fusion gene.

We synthesize the set of three yeast expression constructs pAURHYG(rep)eGFP, pAURHYG(Δ)eGFP, pAURHYG(ins)eGFP, that contain a point mutation at nucleotide 137 of the hygromycin-B coding sequence as follows. (rep) indicates a T137→G replacement, (Δ) represents a deletion of the G137 and (ins) represents an A insertion between nucleotides 136 and 137. We construct this set of plasmids by excising the respective expression cassettes by restriction digest from pHyg(x)EGFP and ligation into pAUR123 (Panvera, CA). We digest 10 µg pAUR123 vector DNA, as well as, 10 µg of each pHyg(x)EGFP construct with KpnI and SalI (NEB). We gel purify each of the DNA fragments and prepare them for enzymatic ligation. We ligate each mutated insert into pHygEGFP vector at 3:1 molar ration using T4 DNA ligase (Roche). We screen clones by restriction digest, confirm by Sanger dideoxy chain termination sequencing and purify using a Qiagen maxiprep kit.

We use this system to assay the ability of five oligonucleotides (shown in Figure 8) to support correction under a variety of conditions. The oligonucleotides which direct correction of the mutation in pAURHYG(rep)GFP can also direct correction of the mutation in pAURHYG(ins)GFP. Three of the four oligonucleotides (HygE3T/25, HygE3T/74 and HygGG/Rev) share the same 25-base sequence surrounding the base targeted for alteration. HygGG/Rev is an RNA-DNA chimeric double hairpin

oligonucleotide of the type described in the prior art. One of these oligonucleotides, HygE3T/74, is a 74-base oligonucleotide with the 25-base sequence centrally positioned. The fourth oligonucleotide, designated HygE3T/74 α , is the reverse complement of HygE3T/74. The fifth oligonucleotide, designated Kan70T, is a non-specific, control oligonucleotide which is not complementary to the target sequence.

5 Alternatively, an oligonucleotide of identical sequence but lacking a mismatch to the target or a completely thioate modified oligonucleotide or a completely 2'-O-methylated modified oligonucleotide may be used as a control.

Oligonucleotide synthesis and cells. We synthesized and purified the chimeric, double-hairpin oligonucleotides and single-stranded oligonucleotides (including those with the indicated modifications) as described in Example 1. Plasmids used for assay were maintained stably in yeast (*Saccharomyces cerevisiae*) strain LSY678 *MAT* α at low copy number under aureobasidin selection. Plasmids and oligonucleotides are introduced into yeast cells by electroporation as follows: to prepare electrocompetent yeast cells, we inoculate 10 ml of YPD media from a single colony and grow the cultures overnight with shaking at 300 rpm at 30°C. We then add 30 ml of fresh YPD media to the overnight cultures and continue shaking at 30°C until the OD₆₀₀ was between 0.5 and 1.0 (3-5 hours). We then wash the cells by centrifuging at 4°C at 3000 rpm for 5 minutes and twice resuspending the cells in 25 ml ice-cold distilled water. We then centrifuge at 4°C at 3000 rpm for 5 minutes and resuspend in 1 ml ice-cold 1M sorbitol and then finally centrifuge the cells at 4°C at 5000 rpm for 5 minutes and resuspend the cells in 120 μ l 1M sorbitol. To transform electrocompetent cells with plasmids or oligonucleotides, we mix 40 μ l of cells with 5 μ g of nucleic acid, unless otherwise stated, and incubate on ice for 5 minutes. We then transfer the mixture to a 0.2 cm electroporation cuvette and electroporate with a BIO-RAD Gene Pulser apparatus at 1.5 kV, 25 μ F, 200 Ω for one five-second pulse. We then immediately resuspend the cells in 1 ml YPD supplemented with 1M sorbitol and incubate the cultures at 30°C with shaking at 300 rpm for 6 hours. We then spread 200 μ l of this culture on selective plates containing 300 μ g/ml 15 hygromycin and spread 200 μ l of a 10⁵ dilution of this culture on selective plates containing 500 ng/ml aureobasidinA and/or and incubate at 30°C for 3 days to allow individual yeast colonies to grow. We then count the colonies on the plates and calculate the gene conversion efficiency by determining the number 20 of hygromycin resistance colonies per 10⁵ aureobasidinA resistant colonies.

Frameshift mutations are repaired in yeast cells. We test the ability of the 30 oligonucleotides shown in Figure 8 to correct a frameshift mutation *in vivo* using LSY678 yeast cells containing the plasmid pAURHYG(ins)GFP. These experiments, presented in Table 6, indicate that these oligonucleotides can support gene correction in yeast cells. These data reinforce the results described in

Example 1 indicating that oligonucleotides comprising phosphorothioate linkages facilitate gene correction much more efficiently than control duplex, chimeric RNA-DNA oligonucleotides. This gene correction activity is also specific as transformation of cells with the control oligonucleotide Kan70T produced no hygromycin resistant colonies above background and thus Kan70T did not support gene correction in this system. In addition, we observe that the 74-base oligonucleotide (HygE3T/74) corrects the mutation in pAURHYG(ins)GFP approximately five-fold more efficiently than the 25-base oligonucleotide (HygE3T/25). We also perform control experiments with LSY678 yeast cells containing the plasmid pAURHYG(wt)GFP. With this strain we observed that even without added oligonucleotides, there are too many hygromycin resistant colonies to count.

We also use additional oligonucleotides to assay the ability of individual oligonucleotides to correct multiple mutations in the pAURHYG(x)eGFP plasmid. These include, for example, one that alters two basepairs that are 3 nucleotides apart is a 74-mer with the sequence 5'-
CTCGTGTTCAGCTTCGATGTAGGAGGGCGTGGTAC**CGTCCTGC****GGGTAAATAGCTGCGCCGATG**
GTTTCTAC-3'; a 74-mer that alters two basepairs that are 15 nucleotides apart with the sequence 5'-
CTCGTGTTCAGCTTCGATGTAGGAGGGCGTGGATA**CGTCCTGC****GGGTAAACAGCTGCGCCGATG**
GTTTCTAC-3'; and a 74-mer that alters two basepairs that are 27 nucleotides apart with the sequence 5'-
CTCGTGTTCAGCTTCGATGTAGGAGGGCGTGGATA**CGTCCTGC****GGGTAAATAGCTGCGCCGACG**
GTTTCTAC. The nucleotides in these oligonucleotides that direct alteration of the target sequence are underlined and in boldface. These oligonucleotides are modified in the same ways as the other oligonucleotides of the invention.

Oligonucleotides targeting the sense strand direct gene correction more efficiently. We compare the ability of single-stranded oligonucleotides to target each of the two strands of the target sequence of both pAURHYG(ins)GFP and pAURHYG(rep)GFP. These experiments, presented in Tables 7 and 8, indicate that an oligonucleotide, HygE3T/74 α , with sequence complementary to the sense strand (i.e. the strand of the target sequence that is identical to the mRNA) of the target sequence facilitates gene correction approximately ten-fold more efficiently than an oligonucleotide, HygE3T/74, with sequence complementary to the non-transcribed strand which serves as the template for the synthesis of RNA. As indicated in Table 7, this effect was observed over a range of oligonucleotide concentrations from 0-3.6 μ g, although we did observe some variability in the difference between the two oligonucleotides (indicated in Table 7 as a fold difference between HygE3T/74 α and HygE3T/74). Furthermore, as shown in Table 8, we observe increased efficiency of correction by HygE3T/74 α relative to HygE3T/74 regardless of whether the oligonucleotides were used to correct the base substitution

mutation in pAURHYG(rep)GFP or the insertion mutation in pAURHYG(ins)GFP. The data presented in Table 8 further indicate that the single-stranded oligonucleotides correct a base substitution mutation more efficiently than an insertion mutation. However, this last effect was much less pronounced and the oligonucleotides of the invention are clearly able efficiently to correct both types of mutations in yeast 5 cells. In addition, the role of transcription is investigated using plasmids with inducible promoters such as that described in Figure 10.

Optimization of oligonucleotide concentration. To determine the optimal concentration of oligonucleotide for the purpose of gene alteration, we test the ability of increasing concentrations of Hyg3T/74 α to correct the mutation in pAURHYG(rep)GFP contained in yeast LSY678. We chose this 10 assay system because our previous experiments indicated that it supports the highest level of correction. However, this same approach could be used to determine the optimal concentration of any given oligonucleotide. We test the ability of Hyg3T/74 α to correct the mutation in pAURHYG(rep)GFP contained in yeast LSY678 over a range of oligonucleotide concentrations from 0-10.0 μ g. As shown in 15 Table 9, we observe that the correction efficiency initially increases with increasing oligonucleotide concentration, but then declines at the highest concentration tested.

Tables are attached hereto.

Table 6

Correction of an insertion mutation in pAURHYG(ins)GFP by HygGG/Rev, HygE3T/25 and HygE3T/74

Oligonucleotide Tested	Colonies on Hygromycin	Colonies on Aureobasidin (/10 ⁵)	Correction Efficiency
HygGG/Rev	3	157	0.02
HygE3T/25	64	147	0.44
HygE3T/74	280	174	1.61
Kan70T	0	—	—

Table 7

An oligonucleotide targeting the sense strand of the target sequence corrects more efficiently.

Amount of Oligonucleotide (μ g)	Colonies per hygromycin plate	
	HygE3T/74	HygE3T/74 α
0	0	0
0.6	24	128 (8.4x)*
1.2	69	140 (7.5x)*
2.4	62	167 (3.8x)*
3.6	29	367 (15x)*

* The numbers in parentheses represent the fold increase in efficiency for targeting the non-transcribed strand as compared to the other strand of a DNA duplex that encodes a protein.

Table 8

Correction of a base substitution mutation is more efficient than correction of a frame shift mutation.

Oligonucleotide Tested (5 µg)	Plasmid tested (contained in LSY678)	
	pAURHYG(ins)GFP	pAURHYG(rep)GFP
HygE3T/74	72	277
HygE3T/74α	1464	2248
Kan70T	0	0

Table 9

Optimization of oligonucleotide concentration in electroporated yeast cells.

Amount (µg)	Colonies on hygromycin	Colonies on aureobasidin (/10 ⁵)	Correction efficiency
0	0	67	0
1.0	5	64	0.08
2.5	47	30	1.57
5.0	199	33	6.08
7.5	383	39	9.79
10.0	191	33	5.79

Example 3 Cultured Cell Manipulation

Mononuclear cells are isolated from human umbilical cord blood of normal donors using Ficoll Hypaque (Pharmacia Biotech, Uppsala, Sweden) density centrifugation. CD34+ cells are immunomagnetically purified from mononuclear cells using either the progenitor or Multisort Kits (Miltenyi Biotec, Auburn, CA). Lin-CD38- cells are purified from the mononuclear cells using negative selection with StemSep system according to the manufacturer's protocol (Stem Cell Technologies, Vancouver, CA).

Cells used for microinjection are either freshly isolated or cryopreserved and cultured in Stem Medium (S Medium) for 2 to 5 days prior to microinjection. S Medium contains Iscoves' Modified Dulbecco's Medium without phenol red (IMDM) with 100 µg/ml glutamine/penicillin/streptomycin, 50 mg/ml bovine serum albumin, 50 µg/ml bovine pancreatic insulin, 1 mg/ml human transferrin, and IMDM; Stem Cell
5 Technologies), 40 µg/ml low-density lipoprotein (LDL; Sigma, St. Louis, MO), 50 mM HEPES buffer and 50 µM 2-mercaptoethanol, 20 ng/ml each of thrombopoietin, flt-3 ligand, stem cell factor and human IL-6 (Pepro Tech Inc., Rocky Hill, NJ). After microinjection, cells are detached and transferred in bulk into wells of 48 well plates for culturing.

35 mm dishes are coated overnight at 4° C with 50 µg/ml Fibronectin (FN) fragment CH-
10 296 (Retronectin; TaKaRa Biomedicals, Panvera, Madison, WI) in phosphate buffered saline and washed with IMDM containing glutamine/penicillin/streptomycin. 300 to 2000 cells are added to cloning rings and attached to the plates for 45 minutes at 37° C prior to microinjection. After incubation, cloning rings are removed and 2 ml of S Medium are added to each dish for microinjection. Pulled injection needles with a range of 0.22 µ to 0.3 µ outer tip diameter are used. Cells are visualized with a microscope equipped
15 with a temperature controlled stage set at 37° C and injected using an electronically interfaced Eppendorf Micromanipulator and Transector. Successfully injected cells are intact, alive and remain attached to the plate post injection. Molecules that are fluorescently labeled allow determination of the amount of oligonucleotide delivered to the cells.

For in vitro erythropoiesis from Lin⁻CD38⁻ cells, the procedure of Malik, 1998 can be used. Cells are cultured in ME Medium for 4 days and then cultured in E Medium for 3 weeks.
20 Erythropoiesis is evident by glycophorin A expression as well as the presence of red color representing the presence of hemoglobin in the cultured cells. The injected cells are able to retain their proliferative capacity and the ability to generate myeloid and erythroid progeny. CD34+ cells can convert a normal A (β^A) to sickle T (β^S) mutation in the β -globin gene or can be altered using any of the oligonucleotides of
25 the invention herein for correction or alteration of a normal gene to a mutant gene. Alternatively, stem cells can be isolated from blood of humans having genetic disease mutations and the oligonucleotides of the invention can be used to correct a defect or to modify genomes within those cells.

Alternatively, non-stem cell populations of cultured cells can be manipulated using any method known to those of skill in the art including, for example, the use of polycations, cationic lipids, liposomes, polyethylenimine (PEI), electroporation, biolistics, calcium phosphate precipitation, or any other method known in the art.
30

Notes on the tables presented below:

Each of the following tables presents, for the specified human gene, a plurality of mutations that are known to confer a clinically-relevant phenotype and, for each mutation, the oligonucleotides that can be used to correct the respective mutation site-specifically in the human genome according to the present invention.

The left-most column identifies each mutation and the clinical phenotype that the mutation confers.

For most entries, the mutation is identified at both the nucleic acid and protein level. At the amino acid level, mutations are presented according to the following standard nomenclature. The centered number identifies the position of the mutated codon in the protein sequence; to the left of the number is the wild type residue and to the right of the number is the mutant codon. Codon numbering is according to the Human Gene Mutation Database, Cardiff, Wales, UK (<http://archive.uwcm.ac.uk/search/mg/allgenes>). Terminator codons are shown as "TERM". At the nucleic acid level, the entire triplet of the wild type and mutated codons is shown.

The middle column presents, for each mutation, four oligonucleotides capable of repairing the mutation site-specifically in the human genome or in cloned human DNA including human DNA in artificial chromosomes, episomes, plasmids, or other types of vectors. The oligonucleotides of the invention, however, may include any of the oligonucleotides sharing portions of the sequence of the 121 base sequence. Thus, oligonucleotides of the invention for each of the depicted targets may be 18, 19, 20 up to about 121 nucleotides in length. Sequence may be added non-symmetrically.

All oligonucleotides are presented, per convention, in the 5' to 3' orientation. The nucleotide that effects the change in the genome is underlined and presented in bold.

The first of the four oligonucleotides for each mutation is a 121 nt oligonucleotide centered about the repair nucleotide. The second oligonucleotide, its reverse complement, targets the opposite strand of the DNA duplex for repair. The third oligonucleotide is the minimal 17 nt domain of the first oligonucleotide, also centered about the repair nucleotide. The fourth oligonucleotide is the reverse complement of the third, and thus represents the minimal 17 nt domain of the second.

The third column of each table presents the SEQ ID NO: of the respective repair oligonucleotide.

EXAMPLE 4
Adenosine Deaminase (ADA)

Adenosine deaminase (ADA, EC 3.5.4.4) catalyses the deamination of adenosine and 2'-deoxyadenosine to inosine or 2'-deoxyinosine respectively. ADA deficiency has been identified as the metabolic basis for 20-30% of cases with recessively inherited severe combined immunodeficiency (SCID). Affected infants are subject to recurrent chronic viral, fungal, protozoal, and bacterial infections and frequently present with persistent diarrhea, failure to thrive and candidiasis. In patients homozygous for ADA deficiency, 2'-deoxyadenosine accumulating during the rapid turnover of cells rich in DNA is converted back to dATP, either by adenosine kinase or deoxycytidine kinase. Many hypotheses have been advanced to explain the specific toxicity to the immune system in ADA deficiency. The apparently selective accumulation of dATP in thymocytes and peripheral blood B cells, with resultant inhibition of ribonucleotide reductase and DNA synthesis is probably the principal mechanism.

The structural gene for ADA is encoded as a single 32 kb locus containing 12 exons. Studies of the molecular defect in ADA-deficient patients have shown that mRNA is usually detectable in normal or supranormal amounts. Specific base substitution mutations have been detected in the majority of cases with the complete deficiency. A C-to-T base substitution mutation in exon 11 accounts for a high proportion of these, whilst a few patients are homozygous for large deletions encompassing exon 1. A common point mutation resulting in a heat-labile ADA has been characterised in some patients with partial ADA deficiency, a disorder with an apparently increased prevalence in the Caribbean.

As yet no totally effective therapy for ADA deficiency has been reported, except in those few cases where bone marrow from an HLA/MLR compatible sibling donor was available.

Two therapeutic approaches have provided long-term benefit in specific instances. First, reconstitution using T cell depleted mismatched sibling marrow has been encouraging, particularly in early presenters completely deficient in ADA. Secondly, therapy with polyethylene glycol-modified adenosine deaminase (PEG-ADA) for more than 5 years has produced a sustained increase in lymphocyte numbers and mitogen responses together with evidence of in vivo B cell function. Success has generally been achieved in late presenters with residual ADA activity in mononuclear cells.

ADA deficiency has been chosen as the candidate disease for gene replacement therapy and the first human experiment commenced in 1990. The clinical consequences of overexpression of ADA activity - one of the potential hazards of gene implant - are known and take the form of an hereditary haemolytic anaemia associated with a tissue-specific increase in ADA activity. The genetic basis for the

latter autosomal dominant disorder seemingly relates to markedly increased levels of structurally normal ADA mRNA.

Table 10
ADA Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency GLN3TERM CAG to TAG	AGAGACCCACCGAGCGGCGGGAGGGAGCAGCGCCGGG CGCACGAGGGCACCATGGCCAGACGCCGCCTCGACAAG CCCAAAGTGAGCGCGCGGGCTCCGGGACGGGGTC	1
	GACCCCCGTCCCCGGAGCCCCCGCGCGCTCACTTGGG CTTGTGAAAGGCGGGCGTCT <u>GGGCCATGGTGCCTCGTGC</u> CCCCGGCGCTGCTCCCTCCGCCGCCGCTCGTGGGTCTCT	2
	CCATGGCCCAGACGCC	3
	GGCGTCT <u>GGGCCATGG</u>	4
Adenosine deaminase deficiency HIS15ASP CAT to GAT	TATTTGTTCTCTCTCCCTTCTCTCTCTCTTCCCCCTGCC CCTTGCAGGTAGAACT <u>G</u> CATGTCCACCTAGACGGATCCATCA AGCCTGAAACCATCTATACTATGGCAGGTAAGTCC	5
	GGACTTACCTGCCATAGTATAAGATGGTTCAGGCTTGATGGA TCCGTCTAGGTGGACAT <u>G</u> CAGTTCTACCTGCAAGGGGGCAG GGGAAGAGAGAGAGAAGGGAGAGAGAGAACAAATA	6
	TAGAACT <u>G</u> CATGTCCAC	7
	GTGGACAT <u>G</u> CAGTTCTA	8
Adenosine deaminase deficiency GLY20ARG GGA to AGA	TCCCTTCTCTCTCTTCCCCCTGCCCTTGAGGTAGAA CTGCATGTCCACCTAGAC <u>GG</u> ATCCATCAAGCCTGAAACCATC TTATACTATGGCAGGTAAGTCCATACAGAACAGGCCCT	9
	AGGGCTTTCTGTATGGACTTACCTGCCATAGTATAAGATGGT TTCAGGCTTGTGGAT <u>CC</u> GTCTAGGTGGACATGCAGTTCTAC CTGCAAGGGGGCAGGGGAAGAGAGAGAGAACAGGA	10
	ACCTAGAC <u>GG</u> ATCCATC	11
	GATGGAT <u>CC</u> GTCTAGGT	12
Adenosine deaminase deficiency GLY74CYS GGC to TGC	CCTGGAGCTCCAAGGGACTTGGGAAGGTTTCCCAACC CCTTCTCCCTCCAGGGCTGCCGGAGGCTATCAAAG GATCGCCTATGAGTTGTAGAGATGAAGGCCAAAGAGG	13

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CCTCTTGGCCTTCATCTCTACAAACTCATAGGCGATCCTTT GATAGCCTCCCGGCAG <u>CCC</u> CTGGGAAGGGAAAGAAAGGGGTT GGGAACAACCTCCCCAAGTCCCTGGGAGCTCCAGG	14
	CTATCGCG <u>GG</u> CTGCCGG	15
	CCGGCAG <u>CCC</u> CGCAGTAG	16
Adenosine Deaminase Deficiency ARG76TRP CGG to TGG	GCTCCAAGGGACTGGGAAGGTTGTTCCAACCCCTTCT TCCCTCCAGGGCTGCCGGGAGGCTATAAAAGGATCGC CTATGAGTTGTAGAGATGAAGGCCAAAGAGGGCGTGG	17
	CCACGCCCTTTGGCCTTCATCTCTACAAACTCATAGGCGAT CCTTTGATAGCCTCCCGCAGCCCCTGGGAAGGGAAAGAAA GGGGTTGGGAACAACCTCCCCAAGTCCCTGGGAGC	18
	GGGGCTGCCGGGAGGCT	19
	AGCCTCCCGCAGCCCC	20
	TTGGGGAAAGGTTGTTCCAACCCCTTCTCCCTCCCAGGG GCTGCCGGGAGGCTATCAA <u>A</u> GGATCGCCTATGAGTTGTAG AGATGAAGGCCAAAGAGGGCGTGGTATGTGGAGGT	21
Adenosine Deaminase Deficiency LYS80ARG AAA to AGA	ACCTCCACATACACCACGCCCTTTGGCCTTCATCTCTACAA ACTCATAGGC <u>G</u> TCTTGTAGCCTCCGGCAGCCCCTGG GAAGGGAAAGAAAGGGTTGGGAACAACCTCCCCAA	22
	GGCTATCAA <u>A</u> GGATCG	23
	CGATCCTTGTAGGCC	24
	GTGTTCCAACCCCTTCTCCCTCCCAGGGCTGCCGGG AGGCTATCAA <u>A</u> GGATCG <u>C</u> CTATGAGTTGTAGAGATGAAGG CCAAAGAGGGCGTGGTATGTGGAGGTGCGGTACAG	25
	CTGTACCGCACCTCACATACACCACGCCCTTTGGCCTTC ATCTCTACAAACTCATAG <u>G</u> CGATCCTTGTAGCCTCCGGC AGCCCCTGGGAAGGGAAAGAAAGGGTTGGGAACAAC	26
Adenosine deaminase deficiency ALA83ASP GCC to GAC	AAGGATCG <u>C</u> CTATGAGT	27
	ACTCATAG <u>G</u> CGATCCTT	28
	AGGCTATCAA <u>A</u> GGATCGCCTATGAGTTGTAGAGATGAAGG CCAAAGAGGGCGTGGT <u>G</u> TCAGTGGAGGTGCGGTACAGTCG CACCTGCTGCCAACTCAAAGTGGAGCCAATCCCCTG	29
	CAGGGGATTGGCTCCACTTGGAGTTGGCCAGCAGGTGCGG ACTGTACCGCACCTCACATACACCACGCCCTTTGGCCTT CATCTCTACAAACTCATAGGC <u>G</u> ATCCTTGTAGCCT	30

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTGGTGT <u>A</u> TGTGGAGG	31
	CCTCCACATACACCACG	32
Adenosine deaminase deficiency ARG101GLN CGG to CAG	GGATCGCCTATGAGTTGTAGAGATGAAGGCCAAAGAGGGCG TGGTGTATGTGGAGGTGC <u>G</u> GTACAGTCCGCACCTGCTGGCC AACTCCAAGTGGAGCCAATCCCCTGGAACCAGGCTGA	33
	TCAGCCTGGTCCAGGGGATTGGCTCCACTTGGAGTTGGCC AGCAGGTGCGGACTGTAC <u>C</u> GCACCTCCACATACACCACGCC CTCTTGGCCTTCATCTACAAACTCATAGGCGATCC	34
	GGAGGTGC <u>G</u> GTACAGTC	35
	GA <u>CT</u> GTAC <u>CG</u> CACCTCC	36
Adenosine deaminase deficiency ARG101LEU CGG to CTG	GGATCGCCTATGAGTTGTAGAGATGAAGGCCAAAGAGGGCG TGGTGTATGTGGAGGTGC <u>G</u> GTACAGTCCGCACCTGCTGGCC AACTCCAAGTGGAGCCAATCCCCTGGAACCAGGCTGA	37
	TCAGCCTGGTCCAGGGGATTGGCTCCACTTGGAGTTGGCC AGCAGGTGCGGACTGTAC <u>C</u> GCACCTCCACATACACCACGCC CTCTTGGCCTTCATCTACAAACTCATAGGCGATCC	38
	GGAGGTGC <u>G</u> GTACAGTC	39
	GA <u>CT</u> GTAC <u>CG</u> CACCTCC	40
	AGGATCGCCTATGAGTTGTAGAGATGAAGGCCAAAGAGGGC GTGGTGTATGTGGAGGTGC <u>G</u> GTACAGTCCGCACCTGCTGGC CAACTCCAAGTGGAGCCAATCCCCTGGAACCAGGCTG	41
Adenosine deaminase deficiency ARG101TRP CGG to TGG	CAGCCTGGTCCAGGGGATTGGCTCCACTTGGAGTTGGCA GCAGGTGCGGACTGTAC <u>C</u> GCACCTCCACATACACCACGCC TCTTGGCCTTCATCTACAAACTCATAGGCGATCC	42
	TGGAGGTGC <u>G</u> GTACAGT	43
	ACTGTAC <u>CG</u> CACCTCCA	44
	ATGAGTTGTAGAGATGAAGGCCAAAGAGGGCGTGGTGTATG TGGAGGTGC <u>G</u> GTACAGTCC <u>C</u> GCACCTGCTGGCCA <u>A</u> CTCCAA GTGGAGCCAATCCCCTGGAACCAGGCTGAGTGAGTGAT	45
Adenosine deaminase deficiency PRO104LEU CCG to CTG	ATCACTCACTCAGCCTGGTCCAGGGGATTGGCTCCACTTG GAGTTGGCCAGCAGGTGC <u>G</u> GTACAGTACCGCACCTCCACATA CACCACGCCCTTTGGCCTTCATCTACAAACTCAT	46
	GTACAGT <u>CC</u> GCACCTGC	47
	GCAGGTGC <u>G</u> GGACTGTAC	48

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency LEU106VAL CTG to GTG	TTTAGAGAGATGAAGGCCAAGAGGGCGTGGTGTATGTGGAG GTGCGGTACAGTCGCAC <u>CT</u> GCTGGCCA <u>CT</u> CCAA <u>GT</u> GGAA GCCAATCCCCTGGAACCAGGCTGAGTGAGTGATGGGCC	49
	GGCCC <u>AT</u> CACTCACTCAGCCTGGTCCAGGGGATTGGCTCCA CTTGGAGTTGGCC <u>AG</u> GTGCGGACTGTACCGCAC <u>CT</u> CC ACATACACCACGCC <u>CT</u> TTGGC <u>CT</u> CATCTACAAA	50
	GTCCGCAC <u>CT</u> GCTGGCC	51
	GGCC <u>AG</u> CAGGTGCGGAC	52
Adenosine deaminase deficiency LEU107PRO CTG to CCG	TAGAGATGAAGGCCAAGAGGGCGTGGTGTATGTGGAGGTG CGGTACAGTCGCAC <u>CT</u> GCTGGCCA <u>CT</u> CCAA <u>GT</u> GGAGCC AATCCCCTGGAACCAGGCTGAGTGAGTGATGGC <u>CT</u> GG	53
	TCCAGGCC <u>AT</u> CACTCACTCAGCCTGGTCCAGGGGATTGGC TCC <u>ACT</u> TTGGAGTTGGCC <u>AG</u> CAGGTGCGGACTGTACCGCAC CTCCACATACACCACGCC <u>CT</u> TTGGC <u>CT</u> CATCTCTA	54
	GCAC <u>CT</u> G <u>CT</u> GGCCA <u>CT</u>	55
	AGTTGGCC <u>AG</u> CAGGTGC	56
Adenosine deaminase deficiency PRO126GLN CCA to CAA	GCCTTC <u>CT</u> TTGCCTCAGGCC <u>AT</u> CC <u>CT</u> ACTCC <u>CT</u> CC <u>CT</u> CAC ACAGAGGG <u>AC</u> CTCAC <u>CC</u> <u>CA</u> GACGAGGTGG <u>CC</u> CTAGTG GGCC <u>AG</u> GGC <u>CT</u> GCAGGAGGGGAG <u>CG</u> GAGACT <u>TC</u> GGGGT	57
	ACCCCG <u>AA</u> GTCTCG <u>CT</u> CCCC <u>CT</u> CTGCAGGCC <u>CT</u> GG <u>CC</u> CAC TAGGG <u>CC</u> ACCAC <u>CT</u> CGT <u>CT</u> <u>GG</u> GTGAGGT <u>CC</u> CT <u>CT</u> GTGTG AGGAGAGGAGTAGGGATGGC <u>CT</u> GAGGCAA <u>AG</u> GAAGG	58
	CCTC <u>AC</u> CC <u>CA</u> GACGAGG	59
	CCTCGT <u>CT</u> <u>GG</u> GTGAGG	60
Adenosine deaminase deficiency VAL129MET GTG to ATG	TTTG <u>C</u> CTCAGGCC <u>AT</u> CC <u>CT</u> ACTCC <u>CT</u> CC <u>CT</u> CACACAGAGGG GAC <u>CT</u> CAC <u>CC</u> CAGACGAG <u>GT</u> GGTGG <u>CC</u> CTAGTGGCC <u>AG</u> GG CCTGCAGGAGGGGAG <u>CG</u> GAGACT <u>TC</u> GGGGT <u>CA</u> GG <u>CC</u>	61
	GGGC <u>CT</u> TGACCC <u>CG</u> AAGTCTCG <u>CT</u> CCCC <u>CT</u> CTGCAGGCC TGG <u>CC</u> CA <u>CT</u> AGGG <u>CC</u> ACC <u>AC</u> CTCGT <u>CT</u> GGGGT <u>GAGG</u> CCCC TCTGTGTGAGGAGAGGAGTAGGGATGGC <u>CT</u> GAGGCAA	62
	CAGACGAG <u>GT</u> GGTGGCC	63
	GGCC <u>AC</u> CC <u>AC</u> CTCGT <u>CT</u> G	64

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency GLY140GLU GGG to GAG	ACAGAGGGGACCTCACCCAGACGAGGTGGTGGCCCTAGTG GGCCAGGGCCTGCAGGAGGGAGCGAGACTTCGGGGTCA AGGCCCGGTCCATCCTGTGCTGCATGCGCCACCAGCCCAG	65
	CTGGGCTGGTGGCGCATGCAGCACAGGATGGACCGGGCCT GACCCGAAGTCTCGCTCCCCCTCCTGCAGGCCCTGGCCA CTAGGGCCACCACCTCGTCTGGGTGAGGTCCCCCTGT	66
	GCAGGAGGGGGAGCGAG	67
	CTCGCTCCCCCTCCTGC	68
5 10	GGGACCTCACCCAGACGAGGTGGTGGCCCTAGTGGCCAG GGCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCC GGTCCATCCTGTGCTGCATGCGCCACCAGCCCAGTGAGTA	69
	TACTCACTGGCTGGTGGCGCATGCAGCACAGGATGGACCG GCCCTTGACCCGAAGTCTCGCTCCCCCTCCTGCAGGCCCT GGCCCACTAGGGCCACCACCTCGTCTGGGTGAGGTCCC	70
	GGGGGAGCGAGACTTCG	71
	CGAAGTCTCGCTCCCCC	72
	GGGGACCTCACCCAGACGAGGTGGTGGCCCTAGTGGCCA GGCCTGCAGGAGGGGGAGCGAGACTTCGGGGTCAAGGCC CGGTCCATCCTGTGCTGCATGCGCCACCAGCCCAGTGAGT	73
15	ACTCACTGGCTGGTGGCGCATGCAGCACAGGATGGACCG GCCCTTGACCCGAAGTCTCGCTCCCCCTCCTGCAGGCCCTG GCCCACTAGGGCCACCACCTCGTCTGGGTGAGGTCCCC	74
	AGGGGGAGCGAGACTTC	75
	GAAGTCTCGCTCCCCCT	76
	TGGTGGCCCTAGTGGCCAGGGCCTGCAGGAGGGGGAGCG AGACTTCGGGGTCAAGGCCCGGTCCATCCTGTGCTGCATGC GCCACCAGCCCAGTGAGTAGGATACCGCCCTGCCAGGG	77
	CCCTGGGCAGGGCGGTGATCCTACTCACTGGCTGGTGGCG CATGCAGCACAGGATGGACCAGGCCCTGACCCGAAGTCTC GCTCCCCCTCCTGCAGGCCCTGGCCACTAGGGCCACCA	78
	CAAGGCCCGGTCCATCC	79
	GGATGGACCGGGCCTTG	80

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency ARG149TRP CGG to TGG	GTGGTGGCCCTAGTGGGCCAGGGCCTGCAGGAGGGGGAGC GAGACTTCGGGTCAAGGCC <u>CGGT</u> CATCCTGTGCTGCATG CGCCACCAGCCCAGTGAGTAGGATCACCGCCCTGCCAGG	81
	CCTGGGCAGGGCGGTGATCCTACTCACTGGGCTGGTGGCGC ATGCAGCACAGGATGGACCG <u>GGC</u> CTTGACCCCCGAAGTCTCG CTCCCCCTCCTGCAGGCCCTGGCCCACTAGGGCCACAC	82
	TCAAGGCC <u>CGGT</u> CATC	83
	GATGGACCGGGCCTTGA	84
Adenosine deaminase deficiency LEU152MET CTG to ATG	CTAGTGGCCAGGGCCTGCAGGAGGGGAGCGAGACTTCG GGGTCAAGGCCCGGTCCATC <u>CTGTGCTGCATGC</u> CCACCAG CCCAGTGAGTAGGATCACCGCCCTGCCAGGGCCGCCGT	85
	ACGGGCGGCCCTGGGCAGGGCGGTGATCCTACTCACTGGG CTGGTGGCGATGCAGCAC <u>AG</u> GATGGACCGGGCCTGACCC CGAAGTCTCGCTCCCCCTCCTGCAGGCCCTGGCCCACTAG	86
	GGTCCAT <u>CTGTGCTGC</u>	87
	GCAGCAC <u>AGG</u> ATGGACC	88
Adenosine deaminase deficiency ARG156CYS CGC to TGC	GGCCTGCAGGAGGGGGAGCGAGACTTCGGGTCAAGGCC GGTCCATCCTGTGCTGCAT <u>GC</u> CCACCAGCCCAGTGAGTAG GATCACCGCCCTGCCAGGGCCGCCGTCTCACCTGGCC	89
	GGCCAGGGTGAGACGGGCGGCCCTGGCAGGGCGGTGATC CTACTCACTGGGCTGGTGGCGATGCAGCACAGGATGGACC GGGCCTTGACCCGAAGTCTCGCTCCCCCTCCTGCAGGCC	90
	GCTGCAT <u>GC</u> CCACCAG	91
	CTGGTGGCGATGCAGC	92
Adenosine deaminase deficiency ARG156HIS CGC to CAC	GCCTGCAGGAGGGGGAGCGAGACTTCGGGTCAAGGCC GTCCATCCTGTGCTGCAT <u>GC</u> CCACCAGCCCAGTGAGTAG ATCACCGCCCTGCCAGGGCCGCCGTCTCACCTGGCC	93
	GGGCCAGGGTGAGACGGGCGGCCCTGGCAGGGCGGTGAT CCTACTCACTGGGCTGGTGGCGATGCAGCACAGGATGGAC GGGCCTTGACCCGAAGTCTCGCTCCCCCTCCTGCAGGC	94
	CTGCAT <u>GC</u> CCACCAGC	95
	GCTGGTGGCGATGCAG	96

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency VAL177MET GTG to ATG	CTGCCACAGACTGGTCCCCAAGGTGGAGCTGTAA GAAGTACCAGCAGCAGACC <u>TGGTAGCCATTGACCTGGCTG</u> GAGATGAGACCATCCCAGGAAGCAGCCTTGCCTGGAC	97
	GTCCAGGCAAGAGGCTGCTCCTGGATGGTCTCATCTCAG CCAGGTCAATGGCTACCACGGTCTGCTGGTACTTCTAC ACAGCTCCACCACCTGGGGGACCAGTCTGTGGGAG	98
	AGCAGACC <u>TGGTAGCC</u>	99
	GGCTACCACGGTCTGCT	100
5 Adenosine deaminase deficiency ALA179ASP GCC to GAC	CAGACTGGTCCCCAAGGTGGAGCTGTGAAGAAGTAC CAGCAGCAGACC <u>TGGTAGCCATTGACCTGGCTGGAGATGA</u> GACCATCCCAGGAAGCAGCCTTGCCTGGACATGTCCA	101
	TGGACATGTCCAGGCAAGAGGCTGCTCCTGGATGGTCTCA TCTCCAGCCAGGTCAATGG <u>CTACCACGGTCTGCTGGTAC</u> TTCTTACACAGCTCCACCACCTGGGGGACCAGTCTG	102
	CGTGGTAG <u>CCATTGACC</u>	103
	GGTCAATGG <u>CTACCACG</u>	104
10 Adenosine deaminase deficiency GLN199PRO CAG to CCG	CCATTGACCTGGCTGGAGATGAGACC <u>ATCCCAGGAAGCAGC</u> CTCTTGCTGGACATGT <u>CCAGGCCTACCAGGTGGTCTGT</u> GAGAAGGAATGGAGAGGCTGGCCCTGGGTGAGCTTGCT	105
	AGACAAGCTCACCCAGGGCCAGCCTCTCCATTCTTCACA GACCCAC <u>CTGGTAGGCCTGGACATGTCCAGGCAAGAGGCT</u> GCTTCTGGATGGTCTCATCTCCAGCCAGGTCAATGG	106
	ACATGT <u>CCAGGCCTACC</u>	107
	GGTAGGC <u>CTGGACATGT</u>	108
15 Adenosine deaminase deficiency ARG211CYS CGT to TGT	GCTAGGGCACCCATGACCTGGCTCTCCCCCTCCAGGAGGC TGTGAAGAGCGGCATT <u>CACCGTACTGTCCACGCCGGGGAGG</u> TGGGCTGGCCGAAGTAGTAAAAGAGGTGAGGGCCTGGG	109
	CCCAGGCC <u>CTCACCTTTACTACTTCGGCCAGCCACCT</u> CCCCGGCG <u>TGGACAGTAC<u>CGTGAATGCCGCTTCAAGCC</u></u> TCCTGGAAAGGGGAGAGCCAGGT <u>CATGGGTGCCCTAGC</u>	110
	GCATT <u>CACCGTACTGTC</u>	111
	GACAGTAC <u>CGGTGAATGC</u>	112

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency ARG211HIS CGT to CAT	CTAGGGCACCCATGACCTGGCTCTCCCCCTTCAGGAGGCTGTGAAGAGCGG GTGAAGAGCGGCATTCACCGTACTGTCCACGCCGGGGAGGT GGGCTCGGCCGAAGTAGTAAAAGAGGTGAGGGCCTGGC	113
	GCCCAGGCCCTCACCTCTTTACTACTTCGGCCGAGCCCACC TCCCCGGCGTGGACAGTACGGTGAATGCCGCTTCAACAGC CTCCTGGAAGGGGGAGAGGCCAGGTATGGGTGCCCTAG	114
	CATTCA <u>CCGTACTGTCC</u>	115
	GGACAGTACGGTGAATG	116
5 03981166827 10	ATGACCTGGCTCTCCCCCTTCAGGAGGCTGTGAAGAGCGG CATTCA <u>CCGTACTGTCCACGCCGGGGAGGTGGGCTGGCCATGGG</u> AAGTAGTAAAAGAGGTGAGGGCCTGGGCTGGCCATGGGG	117
	CCCCATGGCCAGCCCAGGCCCTCACCTCTTTACTACTTCGG CCGAGCCCACCTCCCCGGCGTGGACAGTACGGTGAATGCCG CTCTCACAGCCTGGAAGGGGGAGAGGCCAGGTAT	118
	CTGTCCAC <u>GCCGGGGAG</u>	119
	CTCCCCGGCGTGGACAG	120
	Adenosine deaminase deficiency GLY216ARG GGG to AGG	121
15	ACCTGGCTCTCCCCCTTCAGGAGGCTGTGAAGAGCGGCAT TCACCGTACTGTCCACGCCGGGGAGGTGGGCTGGCCGAAG TAGTAAAAGAGGTGAGGGCCTGGGCTGGCCATGGGTCC	122
	GGACCCCATGGCCAGCCCAGGCCCTCACCTCTTTACTACTT CGGCCGAGCCCACCTCCCCGGCGTGGACAGTACGGTGAATG CCGCTCTCACAGCCTGGAAGGGGGAGAGGCCAGGT	123
	TCCACGCCGGGGAGGTG	124
	CACCTCCCCGGCGTGGA	125
	TGGCTCTCCCCCTTCAGGAGGCTGTGAAGAGCGGCATTCA CCGTACTGTCCACGCCGGGGAGGTGGGCTGGCCGAAGTAG TAAAAGAGGTGAGGGCCTGGGCTGGCCATGGGTCCCTC	126
Adenosine deaminase deficiency GLU217LYS GAG to AAG	GAGGGACCCCATGGCCAGCCCAGGCCCTCACCTCTTTACTA CTTCGGCCGAGCCCACCTCCCCGGCGTGGACAGTACGGTGA ATGCCGCTTACAGCCTGGAAGGGGGAGAGCCA	127
	ACGCCGGGGAGGTGGC	128
	GCCCACCTCCCCGGCGT	

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency THR233ILE ACA to ATA	CTGCCTCCTCCCATACTGGCTTATTCTGCTTCTACAGGC TGTGGACATACTCAAGACAGAGCGGCTGGGACACGGCTACC ACACCCCTGGAAGACCAGGCCCTTATAACAGGCTGCG	129
	CGCAGCCTGTTATAAAGGGCCTGGTCTTCCAGGGTGTGGTAG CCGTGTCCTCAGCCGCTCTGTCTTGAGTATGTCCACAGCCTGT AGAGAAGCAGAACAGAGCCAAGTATGGGAGGAGGCAG	130
	ACTCAAGACAGAGCGGC	131
	GCCGCTCTGTCTTGAGT	132
5 Adenosine deaminase deficiency ARG253PRO CGG to CCG	CAGAGCGGCTGGGACACGGCTACCACACCCTGGAAGACCAG GCCCTTATAACAGGCTGC <u>GG</u> CAGGAAAACATGCACTTCGAG GTAAGCGGGCCAGGGAGTGGGGAGGAACCATCCCCGGC	133
	GCCGGGGATGGTTCTCCCCACTCCCTGGCCCGCTTACCTC GAAGTGCATGTTTCTGCC <u>GC</u> CAGCCTGTTATAAAGGGCTG GTCTTCCAGGGTGTGGTAGCCGTGTCCCAGCCGCTCTG	134
	CAGGCTGC <u>GG</u> CAGGAAA	135
	TTTCCTGCC <u>GC</u> CAGCCTG	136
	GAGCGGCTGGGACACGGCTACCACACCCTGGAAGACCAGGC CCTTATAACAGGCTGC <u>GG</u> CAGGAAAACATGCACTTCGAGGT AAGCGGGCCAGGGAGTGGGGAGGAACCATCCCCGGCTG	137
10 Adenosine deaminase deficiency GLN254TERM CAG to TAG	CAGCCGGGGATGGTTCTCCCCACTCCCTGGCCCGCTTACC TCGAAGTGCATGTTTCTGCC <u>GC</u> CAGCCTGTTATAAAGGGCC TGGTCTTCCAGGGTGTGGTAGCCGTGTCCCAGCCGCTC	138
	GGCTGC <u>GG</u> CAGGAAAAC	139
	GT <u>TTT</u> CCTGCC <u>GC</u> CAGCC	140
	CCACACACCTGCTTCCAGATCTGCCCTGGTCCAGCTACC TCACTGGTGCTGGAAAG <u>CC</u> GGACACGGAGCATGCAGTCATT CGGTGAGCTCTGTTCCCTGGCCTGTTCAATTGTT	141
	AACAAAATTGAACAGGCCAGGGGAACAGAGCTACCGAATG ACTGCATGCTCCGTGTCC <u>GG</u> CTTCCAGGCACCAGTGAGGTA GCTGGACCAGGGCAGATCTGGAAGAGCAGGTGTGG	142
15 Adenosine deaminase deficiency PRO274LEU CCG to CTG	CTGGAAG <u>CC</u> GGACACGG	143
	CCGTGTCC <u>GG</u> CTTCCAG	144

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenosine deaminase deficiency SER291LEU TCG to TTG	GGAGGCTGATTCTCCTCCCTCTGCAGGCTAAAA ATGACCAGGCTAACTACT <u>CGCTCAACACAGATGACCGCTCA</u> TCTTCAGTCCACCCCTGGACACTGATTACCAGATGAC	145
	GTCATCTGGAATCAGTGTCCAGGGTGGACTTGAAGATGAGC GGGTCACTGTGTTGAGC <u>GAGTAGTTAGCCTGGTCATTTTGAGC</u> GCCTGCAGAAGAGGGAGGGAGAGAATCAGCCTCC	146
	TAACTACT <u>CGCTCAACA</u>	147
	TGTTGAGC <u>GAGTAGTTA</u>	148
5 10	CCTCCCTCTTCAGGCTAAAAATGACCAGGCTAACTACT CGCTCAACACAGATGACCC <u>GCTCATCTCAAGTCCACCCCTGG</u> ACACTGATTACCAGATGACCAAACGGGACATGGCCTT	149
	AAGCCCAGTCCC GTTGGTCATCTGGTAATCAGTGTCCAGG GTGGACTTGAAGATGAGC <u>GGGTCACTGTGTTGAGCGAGTAG</u> TTAGCCTGGTCATTTGAGCCTGCAGAAGAGGGAGG	150
	AGATGAC <u>CCGCTCATCT</u>	151
	AGATGAG <u>CGGGTCATCT</u>	152
	AAAATGACCAGGCTAACTACT <u>CGCTCAACACAGATGACCCGC</u> TCATCTTCAGTCCACCC <u>CTGGACACTGATTACCAGATGACCAA</u> ACGGGACATGGGCTTACTGAAGAGGGAGTTAAAAG	153
15	CTTTAAACTCCTCTTCAGTAAAGCCCAGTCCC GTTGGTCATCTGGTAATCAGTGTCC <u>AGGGTGGACTTGAAGATGAGCGGGT</u> CATCTGTGTTGAGC <u>GAGTAGTTAGCCTGGTCATTT</u>	154
	GTCCAC <u>CCCTGGACACTG</u>	155
	CAGTGTCC <u>AGGGTGGAC</u>	156
	GCCTTCTTGTCTGGTCATGTTGCTGCCATTCTGCC TTCCAGAACATCAAT <u>CGGGCCAATCTAGTTCCCTCCAGAA</u> GATGAAAAGAGGGAGCTCTCGACCTGCTATAA	157
	TTATAGAGCAGGTGAGAACAGCTCCCTTTCATCTTCTGGGA GGAAACTAGATTGCC <u>GCATTGATGTTCTGGAAAGGCCAGA</u> ATGGCAGACAA <u>CATGGAACCAGAGAACAAAGAAGGC</u>	158
C-to-T at base 1081	CATCAAT <u>CGGGCCAAT</u>	159
	ATTGGCC <u>GCATTGATG</u>	160

EXAMPLE 5
P53 Mutations

The p53 gene codes for a protein that acts as a transcription factor and serves as a key regulator of the cell cycle. Mutation in this gene is probably the most significant genetic change characterizing the transformation of cells from normalcy to malignancy.

Inactivation of p53 by mutation disrupts the cell cycle which, in turn, sets the stage for tumor formation. Mutations in the p53 gene are among the most commonly diagnosed genetic disorders, occurring in as many as 50% of cancer patients. For some types of cancer, most notably of the breast, lung and colon, p53 mutations are the predominant genetic alterations found thus far. These mutations are associated with genomic instability and thus an increased susceptibility to cancer. Some p53 lesions result in malignancies that are resistant to the most widely used therapeutic regimens and therefore demand more aggressive treatment.

That p53 is associated with different malignant tumors is illustrated in the Li-Fraumeni autosomal dominant hereditary disorder characterized by familial multiple tumors due to mutation in the p53 gene. Affected individuals can develop one or more tumors, including: brain (12%); soft-tissue sarcoma (12%); breast cancer (25%); adrenal tumors (1%); bone cancer (osteosarcoma) (6%); cancer of the lung, prostate, pancreas, and colon as well as lymphoma and melanoma can also occur.

Certain of the most frequently mutated codons are codons 175, 248 and 273, however a variety of oligonucleotides are described below in the attached table.

Table 11
p53 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
In 2 families with Li-Fraumeni syndrome, there was a C-to-T mutation at the first nucleotide of codon 248 which changed arginine to tryptophan.	GAATGTACCACCATCCACTACAACATACATGTGTAACAGTTCT GCATGGCGGGCATGAAC <u>CCGGAGGCCATCCTCACCATCATC</u> ACACTGGAAGACTCCAGGTCAAGGAGCCACTTGCACC	161
	GGTGGCAAGTGGCTCCTGACCTGGAGTCTTCAGTGTGATGA TGGTGAGGATGGGCTCC <u>GTTCATGCCGCCATGCAGGAA</u> CTGTTACACATGTAGTTGATGGATGGTGGTACAGTC	162
	GCATGAAC <u>CCGGAGGCC</u>	163

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GGGCCTCC <u>G</u> TTCATGC	164
5 In a family with the Li-Fraumeni syndrome, a G-to-A mutation at the first nucleotide of codon 258 resulting in the substitution of lysine for glutamic acid.	TGTAAACAGTTCTGCATGGCGGCATGAACCAGGAGGCCAT CCTCACCATCATCACACT <u>GG</u> AAGACTCAGGTCAAGGAGCCAC TTGCCACCCCTGCACACTGGCCTGCTGTGCCCGAGCCTC	165
	GAGGCTGGGGCACAGCAGGCCAGTGTGCAGGGTGGCAAGT GGCTCCTGACCTGGAGTCT <u>CC</u> AGTGTGATGATGGTGAGGAT GGGCCTCC <u>G</u> TTCATGCCGCCATGCAGGA <u>CT</u> GTTACA	166
	TCACACT <u>G</u> AAGACTCC	167
	GGAGTCT <u>CC</u> AGTGTGA	168
10 In a family with the Li-Fraumeni syndrome, a G-to-T mutation at the first nucleotide of codon 245 resulting in the substitution of cysteine for glycine.	GTTGGCTCTGACTGTACCACCATCCACTACA <u>ACTACATGTGTA</u> ACAGTTCTGCATGGCGGCATGAACCAGGAGGCCATCCTC ACCATCATCACACTGGAA <u>AGACTCCAGGTCA</u> GGAGCCA	169
	TGGCTCCTGACCTGGAGTCTCCAGTGTGATGATGGTGAGGA TGGGCCTCCGGTT <u>CATGCCGCC</u> ATGCAGGA <u>ACTGTTACACA</u> TGTAGTTGAGTGGATGGTGGTACAGTCAGAGCCAAC	170
15 A gly245-to-ser, GGC-to-AGC, mutation was found in a patient in whom osteosarcoma was diagnosed at the age of 18 years.	GCATGGGC <u>GG</u> CATGAAC	171
	GTT <u>CATGCCGCC</u> CATGC	172
	TCCACTACA <u>ACTACATGTGTA</u> ACAGTTCTGCATGGCGGC TGAACCGGAGGCC <u>CATCCT</u> ACCATCATCACACTGGAA <u>AGACT</u> CCAGGTCA <u>GGAGCC</u> ACTGCCACCC <u>CTGCACACTGGCC</u>	173
20 25 30 In a family with the Li-Fraumeni syndrome, a germline mutation at codon 252: a T-to-C change at the second position resulted in substitution of proline for leucine.	GGCCAGTGTGCAGGGTGGCAAGTGGCTCTGACCTGGAGTC TTCCAGTGTGATGATGGT <u>AGGATGGCCTCCGGTT</u> CATGCC GCCCATGCAGGA <u>ACTGTTACACATGTAGTTAGTGG</u> A	174
	GCCC <u>CATCCT</u> ACCATCA	175
	TGATGGT <u>GAGGATGGC</u>	176

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Researchers analyzed for mutations in p53 hepatocellular carcinomas from patients in Qidong, an area of high incidence in China, in which both hepatitis B virus and aflatoxin B1 are risk factors. Eight of 16 tumors had a point mutation at the third base position of codon 249. The G-to-T mutation at codon 249 led to a change from arginine to serine (AGG to AGT).	TACCACCATCCACTACAACATGTGTAACAGTCCTGCATGGCGCATGAACCGGAGGCCATCCTCACCATCACACTGGAAGACTCCAGGTCAAGGAGCCACTTGCCACCCCTGCA	177
	TGCAGGGTGGCAAGTGGCTCTGACCTGGAGTCTTCAGTGATGATGGTGAAGGATGGG <u>C</u> CTCCGGTTCATGCCGCCATGCAGGAACGTACACATGTAGTTAGTGGATGGTGGTA	178
	AACCGGAG <u>G</u> CCCATCCT	179
	AGGATGGG <u>C</u> CTCCGGTT	180
In cases of hepatocellular carcinoma in southern Africa, a G-to-T substitution in codon 157 resulting in a change from valine to phenylalanine.	CTGGCCAAGACCTGCCCTGTGCAGCTGTGGTTGATTCCACA CCCCCGCCCGGCACCCGC <u>G</u> TCCGCGCCATGGCCATCTACAA GCAGTCACAGCACATGACGGAGGTTGTGAGGCCTGCCC	181
	GGCAGCGCCTCACAA <u>C</u> CTCCGTCAATGTGCTGTGACTGCTGTAGATGGCCATGGCGCGAGCAGCAGGGTGCAGGGCGGGGGTGTGGAATCAACCCACAGCTGCACAGGGCAGGTCTGGCCAG	182
	GCACCCGC <u>G</u> GTCCGCAGCC	183
	GGCGCGGAC <u>G</u> CGGGGTGC	184
In a family with Li-Fraumeni in which noncancerous skin fibroblasts from affected individuals showed an unusual radiation-resistant phenotype, a point mutation in codon 245 of the P53 gene. A change from GGC to GAC predicted substitution of aspartic acid for glycine.	TTGGCTCTGACTGTACCACCATCCACTACAACATGTGAA CAGTCCTGCATGGCGGCATGAACCGGAGGCCATCCTACACCATCATCACACTGGAAGACTCCAGGTCAAGGAGCCAC	185
	GTGGCTCCTGACCTGGAGTCTCCAGTGTGATGGTGAAGGATGGGCTCCGGTTCA <u>T</u> GCAGGAAC <u>T</u> GTTACACATGTAGTTAGTGGATGGTGGTACAGTCAGAGCCAA	186
	CATGGGCG <u>G</u> CATGAACC	187
	GGTT <u>C</u> ATGC <u>C</u> CGCCCATG	188

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
5 In 2 of 8 families with Li-Fraumeni syndrome, a mutation in codon 248: a CGG-to-CAG change resulting in substitution of glutamine for arginine.	ACTGTACCACCATCCACTACAACATGTGTAACAGTCTCG CATGGCGGCATGAACCGGGAGGCCATCCTCACCATCATCA CACTGGAAGACTCCAGGTAGGAGGCCATTGCCACCC	189
	GGGTGGCAAGTGGCTCTGACCTGGAGTCTCCAGTGTGAT GATGGTGAGGATGGCCTCCGGTTATGCCGCCATGCAGG AACTGTTACACATGTAGTTAGTGGATGGTGGTACAGT	190
	CATGAACC <u>GG</u> GAGGCCA	191
	TGGGC <u>CTCCGG</u> TTCATG	192
10 In 9 members of an extended family with Li-Fraumeni syndrome, a germline mutation at codon 133 (ATG-to-ACG), resulted in the substitution of threonine for methionine (M133T), and completely cosegregated with the cancer syndrome.	CCCTGACTTCAACTCTGTCTCCTCTTCCTACAGTACTC CCCTGCCCTAACAAAGAT <u>GT</u> TTTGCCA <u>AC</u> TTGGCCAAGACCTG CCCTGTGCAGCTGTGGTTGATTCCACACCCCCGCC	193
	GGCGGGGGTGTGGAATCAACCCACAGCTGCACAGGGCAGGT CTTGGCCAGTTGGCAA <u>AC</u> <u>AT</u> CTTGTGAGGGCAGGGGAGTA CTGTAGGAAGAGGAAGGAGACAGAGTTGAAAGTCAGGG	194
	CAACAAG <u>AT</u> TTTGCC	195
	GGCAA <u>AAAC</u> <u>AT</u> CTTGTG	196
15 20 25 In 1 pedigree consistent with the Li-Fraumeni syndrome, a germline G-to-T transversion at codon 272 (valine to leucine) was found.	TCTTGCTTCTCTTCCATCCTGAGTAGTGGTAATCTACTGG GACGGAACAGCTTGAG <u>GT</u> CGTGTGGCCTGCTGGGA GAGACC <u>GGCG</u> CACAGAGGAAGAGAAC <u>CT</u> CCGCAAGA	197
	TCTTGCGGAGATTCTTCCCTGTGCGCCGGTCTCTCCAG GACAGGCACAAACACGC <u>AC</u> <u>CT</u> CAAAGCTGTTCCGTCCCAGTA GATTACCAACTCAGGATAGGAAAAGAGAAGCAAGA	198
	GCTTGAG <u>GT</u> CGTGT	199
	AACACGC <u>AC</u> <u>CT</u> CAAAGC	200
30 35 A ser241-to-phe mutation due to a TCC-to-TTC change was found in a patient with hepatoblastoma and multiple foci of osteosarcoma.	TTATCTCCTAGGTTGGCTCTGACTGTACCAACCATCCACTACAA CTACATGTGTAACAGT <u>CT</u> GCATGGCGGCATGAACCGGAG GCCCATCCTCACCATCATCACACTGGAAGACTCCAG	201
	CTGGAGTCTCCAGTGTGATGGTGGAGATGGCCTCCG GTTCATGCCGCCATGCAG <u>GA</u> <u>CT</u> GTTACACATGTAGTTGTA GTGGATGGTGGTACAGTCAGAGCCAACCTAGGAGATAA	202

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:	
	TAACAGTT <u>C</u> CTGCATGG	203	
	CCATGCAG <u>G</u> AACTGTTA	204	
5 10 15 20	An AAG-to-TAG change of codon 120, resulting in conversion from lysine to a stop codon, was found in a patient with osteosarcoma and adenocarcinoma of the lung at age 18 and brain tumor (glioma) at the age of 27.	CAGAAAACCTACCAGGGCAGCTACGGTTCCGTCTGGGCTTC TTGCATTCTGGGACAG <u>C</u> AAGTCTGTGACTTGACCGGTCA GTGCCCTGAGGGGCTGGCTTCATGAGACTTCAATGCC	205
		GGCATTGAAGTCTCATGGAAGGCCAGCCCCTCAGGGCAACTG ACCGTGCAAGTCACAGACT <u>T</u> GGCTGTCCCAGAACATGCAAGAACG CCCAGACGGAAACCGTAGCTGCCCTGGTAGGTTTCTG	206
		GGACAG <u>C</u> CAAGTCTGTG	207
		CACAGACT <u>T</u> GGCTGTCC	208
25	A CGG-to-TGG change at codon 282, resulting in the substitution of tryptophan for arginine, was found in a patient who developed osteosarcoma at the age of 10 years.	GGTAATCTACTGGGACGGAACAGCTTGAGGTGCGTGTGGT GCCTGTCTGGGAGAGAC <u>C</u> GGCGCACAGAGGAAGAGAACATCT CCGCAAGAAAGGGGAGCCTCACACGAGCTGCCCTCAG	209
		CTGGGGGCAGCTCGTGGTGAGGCTCCCCTTCTGCGGAGA TTCTCTTCTCTGTGCGCC <u>G</u> TCTCTCCAGGACAGGCACAA ACACGCACCTCAAAGCTGTTCCGTCCCAGTAGATTACC	210
		GGAGAGAC <u>C</u> GGCGCACA	211
		TGTGCGCC <u>G</u> TCTCTCC	212
25	In 5 of 6 anaplastic carcinomas of the thyroid and in an anaplastic carcinoma thyroid cell line ARO, a CGT-to-CAT mutation converted arginine-273 to histidine.	GCTTCTCTTCCATCCTGAGTAGTGGTAATCTACTGGGACG GAACAGCTTGAGGTGCG <u>T</u> GTGGCTGCCTGTCCTGGGAGAGA CCGGCGCACAGAGGAAGAGAACATCCGCAAGAAAGG	213
		CCTTCTTGCAGGAGATTCTCTCCTCTGTGCGCCGGTCTCTC CCAGGACAGGCACAAACAC <u>G</u> CACCTCAAAGCTGTTCCGTCCC AGTAGATTACCACTACTCAGGATAGGAAAAGAGAAC	214
		TGAGGTGCG <u>T</u> GTGGT	215
		CACAAACAC <u>G</u> CACCTCA	216

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
5 A germline GGA-to-GTA mutation resulting in a change of glycine-325 to valine was found in a patient who had non-Hodgkin lymphoma diagnosed at age 17 and colon carcinoma at age 26.	TCCTAGCACTGCCAACAAACACCAGCTCCTCTCCCCAGCCAA AGAAGAAACC <u>ACTGGATG</u> GAGAATATTCACCC <u>T</u> TCAGGTACT AAGTCTTGGGACCTCTTATCAAGTGGAAAGTTCCA	217
	TGGAAACTTCCACTTGATAAGAGGTCCCAGACTTAGTACCT GAAGGGTGAATATT <u>CTC</u> CATCCAGTGGTTCTCTGGCTG GGGAGAGGAGCTGGTGTGGCAGTGCTAGGA	218
	ACTGGAT <u>G</u> GAGAATATT	219
	AATATT <u>CTC</u> CATCCAGT	220
10 CGC-CCC Arg-72 to Pro association with Lung cancer	AATGGTTCACTGAAGACCCAGGTCCAGATGAAGCTCCCAGAA TGCCAGAGGCTGCTCCCC <u>G</u> CGTGGCCCTGCACCAGCAGCT CCTACACCGGCGGCCCTGCACCAGCCCCCTCTGGCC	221
	GGCCAGGAGGGGGCTGGTGCAGGGGCCGCCGGTAGGAG CTGCTGGTGCAGGGGCCACG <u>C</u> GGGGAGCAGCCTCTGGCATT CTGGGAGCTTCATCTGGACCTGGTCTTCAGTGAACCATT	222
	TGCTCCCC <u>G</u> CGTGGCCC	223
	GGGCCACGGCGGGGAGCA	224
15 CCG-CTG Pro-82 to Leu Breast cancer	AAGCTCCCAGAATGCCAGAGGGCTGCTCCCCGCGTGGCCCT GCACCA <u>CG</u> AGCTCCTACACCGGCCGCCCTGCACCAGCCCC CTCCTGGCCCTGTCA <u>T</u> CTGTCCCTCCCAGAAAAC	225
	GT <u>TTT</u> CTGGGAAGGGACAGAAGATGACAGGGGCCAGGAGGG GGCTGGTGCAGGGGCCGCCGGTAGGAGCTGCTGGTCA GGGCCACGCGGGAGCAGCCTCTGGCATTCTGGAGCTT	226
	TCCTACAC <u>CG</u> GGGCC	227
	GGGCCGCCGGTAGGA	228
20 cCAA-TAA Gln-136 to Ter Li-Fraumeni syndrome	TTCAACTCTGTCTCCTCCTTCCACTACAGTACTCCCCTGCC TCAACAAGAT <u>GT</u> TTT <u>G</u> CCAACTGGCCAA <u>GA</u> CTGCC <u>T</u> GTGC AGCTGTGGTTGATTCCACACCCCCGCCGGCACCC	229
	GGGTGCCGGGCGGGGGTGTGGAATCAACCCACAGCTGCACA GGCAGGTCTGGCCAGTT <u>GG</u> CAAACATCTGTTGAGGGCA GGGGAGTACTGTAGGAAGAGGAAGGAGACAGAGTTGAA	230
	TGTTT <u>G</u> CCAACTGGCC	231
	GGCCAGTT <u>GG</u> CAAACA	232

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
TGC-TAC Cys-141 to Tyr Li-Fraumeni syndrome	TCCTCTTCTACAGTACTCCCCTGCCCTCAACAAGATGTTTG CCA ACTGGCCAAGACCT <u>GCCCTGTGCAGCTGTGGTTGATT</u> CACACCCCCGCCGGCACCGCGTCCGCGCCATGGC	233
	GCCATGGCGCGGACGCCGGTGCAGGGGGGTGTGGAAT CAACCCACAGCTGCACAGGG <u>CAGGTCTTGGCCAGTTGGCAA</u> AACATCTTGTGAGGGCAGGGGAGTACTGTAGGAAGAGGA	234
	CAAGACCT <u>GCCCTGTGC</u>	235
	GCACAGGG <u>CAGGTCTT</u> G	236
aCCC-TCC Pro-151 to Ser Li-Fraumeni syndrome	AACAAGATGTTTGCCA <u>ACTGGCCAAGACCTGCCCTGTGCAG</u> CTGTGGTTGATTCCAC <u>ACCCCCGCCGGCACCCGCGTCCG</u> CGCCATGCCATCTACAAGCAGTCACAGCACATGACGG	237
	CCGTCATGTGCTGTGACTGCTTGTAGATGCCATGGCGCGG ACGCGGGTGC <u>CCGGGCGGGGTGTGGAATCAACCCACAGCT</u> GCACAGGGCAGGTCTTGGCCAGTTGGCAAAACATCTTGT	238
	ATTCCACAC <u>CCCCCGCCC</u>	239
	GGGCGGGGGTGTGGAAT	240
CCG-CTG Pro-152 to Leu Adrenocortical carcinoma	AGATGTTTGCCA <u>ACTGGCCAAGACCTGCCCTGTGCAGCTGT</u> GGGTTGATTCCAC <u>ACCCCCGCCGGCACCCGCGTCCGCGCC</u> ATGCCCATCTACAAGCAGTCACAGCACATGACGGAGGT	241
	ACCTCCGT <u>CATGTGCTGTGACTGCTTGTAGATGCCATGGCG</u> CGGACGCGGGTGC <u>CCGGGCGGGGTGTGGAATCAACCCACA</u> GCTGCACAGGGCAGGTCTTGGCCAGTTGGCAAAACATCT	242
	CACACCCC <u>GCCCGGGCA</u>	243
	TGCCGGG <u>CGGGGTGTG</u>	244
GGC-GTC Gly-154 to Val Glioblastoma	TTTGCCA <u>ACTGGCCAAGACCTGCCCTGTGCAGCTGTGGTTG</u> ATTCCACACCCCCCGCCCG <u>GACCCGCGTCCGCGCCATGGCC</u> ATCTACAAGCAGTCACAGCACATGACGGAGGTGTGAG	245
	CTCACAA <u>CTCCGTATGTGCTGTGACTGCTTGTAGATGCC</u> ATGGCGCGGACGCGGGTGC <u>CCGGGCGGGGTGTGGAATCAA</u> CCCACAGCTGCACAGGGCAGGTCTTGGCCAGTTGGCAAA	246
	CCCGCCCG <u>GACCCGCG</u>	247
	CGCGGGTGC <u>CCGGGCGGG</u>	248
CGC-UAC Arg-175 to His Li-Fraumeni syndrome	CCCGCGTCCGCGCCATGCCCATCTACAAGCAGTCACAGCAC ATGACGGAGGTGTGAGGC <u>GCTGCC</u> CCACCATGAGCGCTG CTCAGATAGCGATGGTGAGCAGCTGGGGCTGGAGAGACG	249

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTCTCTCCAGCCCCAGCTGCTCACCATCGCTATCTGAGCAG CGCTCATGGTGGGGGCAG <u>C</u> GCCTCACAAACCTCCGTATGTG CTGTGACTGCTTGAGATGGCCATGGCGCGGACGCGGG	250
	TGTGAGGC <u>G</u> CTGCC	251
	GGGGCAG <u>C</u> GCCTACA	252
tGAG-AAG Glu-180 to Lys Li-Fraumeni syndrome	ATGGCCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTG AGGCGCTGCC CCCCACCAT <u>G</u> AGCGCTGCTCAGATAGCGATGG TGAGCAGCTGGGCTGGAGAGACGACAGGGCTGGTTGC	253
	GCAACCAGCCCTGCGTCTCTCCAGCCCCAGCTGCTCACCAT CGCTATCTGAGCAGCGCT <u>C</u> ATGGTGGGGCAGCGCCTACA ACCTCCGTATGTGCTGTGACTGCTTGAGATGCCAT	254
	CCCACCAT <u>G</u> AGCGCTGC	255
	GCAGCGCT <u>C</u> ATGGTGGG	256
	GCCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTGAGG CGCTGCC CCCCACCAT <u>G</u> AGCGCTGCTCAGATAGCGATGGTGA GCAGCTGGGCTGGAGAGACGACAGGGCTGGTTGCCA	257
gCGC-TGC Arg-181 to Cys Breast cancer	TGGGCAACCAGCCCTGCGTCTCTCCAGCCCCAGCTGCTCA CCATCGCTATCTGAGCAGC <u>G</u> CTCATGGTGGGGCAGCGCCT CACAAACCTCCGTATGTGCTGTGACTGCTTGAGATGGC	258
	ACCATGAG <u>C</u> GCTGCTCA	259
	TGAGCAGCGCTCATGGT	260
	CCATCTACAAGCAGTCACAGCACATGACGGAGGTTGTGAGGC GCTGCC CCCCACCAT <u>G</u> AGCGCTGCTCAGATAGCGATGGTGAG CAGCTGGGCTGGAGAGACGACAGGGCTGGTTGCCAG	261
CGC-CAC Arg-81 to His Breast cancer	CTGGGCAACCAGCCCTGCGTCTCTCCAGCCCCAGCTGCTC ACCATCGCTATCTGAGCAGC <u>G</u> CTCATGGTGGGGCAGCGCC TCACAAACCTCCGTATGTGCTGTGACTGCTTGAGATGG	262
	CCATGAG <u>C</u> GCTGCTCAG	263
	CTGAGCAG <u>C</u> GCTCATGG	264
	CCAGGGTCCCCAGGCCTCTGATTCTCACTGATTGCTCTTAG GTCTGGCCCTCCTCAG <u>C</u> ATCTTATCCGAGTGGAAAGGAAATT TGCCTGTGGAGTATTGGATGACAGAACACTTTCG	265
CAT-CGT His-193 to Arg Li-Fraumeni syndrome	CGAAAAGTGTCTGTCACTCAAATACTCCACACGCAAATTTC CTTCCACTCGGATAAGATGCTGAGGAGGGGCCAGACCTAAGA GCAATCAGTGGAAATCAGAGGCCTGGGACCTGG	266

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCCTCAGCA <u>T</u> CTTATCC	267
	GGATAAGA <u>T</u> GCTGAGGA	268
cCGA-TGA Arg-196 to Term Adrenocortical carcinoma	CCCAGGCCTCTGATTCCCTACTGATTGCTCTTAGGTCTGGCC CCTCCTCAGCATCTTAT <u>CC</u> GAGTGGAAAGGAAATTGCGTGTG GAGTATTGGATGACAGAAACACTTTGACATAGTG	269
	CACTATGTCGAAAAGTGTTCCTGTCATCCAAATACTCCACACG CAAATTCCCTCCACT <u>CG</u> GATAAGATGCTGAGGAGGGGCCAG ACCTAAGAGCAATCA <u>T</u> GAGGAATCAGAGGCCTGGG	270
	ATCTTAT <u>CC</u> GAGTGGAA	271
	TTCCACT <u>CG</u> GATAAGAT	272
	GCCCCCTCCTCAGCATCTTATCCGAGTGGAAAGGAAATTGCGT GTGGAGTATTGGATGAC <u>A</u> AGAAACACTTTGACATAGTG GTGGTGCCTATGAGCCGCCTGAGGTCTGGTTGCAA	273
cAGA-TGA Arg-209 to Term Li-Fraumeni syndrome	TTGCAAACCAGACCTCAGGCCGCTCATAGGGCACCA CTATGTCGAAAAGTGTTC <u>T</u> GTCATCCAAATACTCCACACGCA AATTCCCTCCACTCGGATAAGATGCTGAGGAGGGC	274
	TGGATGAC <u>A</u> AGAAACACT	275
	AGTGTTC <u>T</u> GTCATCCA	276
	CATCTTATCCGAGTGGAAAGGAAATTGCGTGTGGAGTATTG GATGACAGAAACACTTT <u>C</u> GACATAGTGTGGTGGTGCCTAT GAGCCGCCTGAGGTCTGGTTGCAACTGGGTCTCTG	277
tCGA-TGA Arg-213 to Term Li-Fraumeni syndrome	CAGAGACCCCAGTTGCAAACCAGACCTCAGGCCGCTCATAG GGCACCA ACTCCACACGCAAATTCCCTCCACTCGGATAAGATG	278
	ACACTTT <u>C</u> GACATAGT	279
	ACTATGTC <u>G</u> AAAAGTGT	280
	GGAAATTGCGTGTGGAGTATTGGATGACAGAAACACTTT GACATAGTGTGGTGGTGCCTATGAGCCGCCTGAGGTCTGG TTGCAACTGGGTCTCTGGGAGGAGGGTTAAGGGT	281
gCCC-TCC Pro-219 to Ser Adrenocortical carcinoma	ACCCCTAACCCCTCCCTCCAGAGACCCCAGTTGCAAACCA GAGCCTCAGGCCGCTCATAGGGCACCA ACTATGTC <u>G</u> AAAAG TGTTCTGTCATCCAAATACTCCACACGCAAATTCC	282
	TGGTGGTGCCTATGAG	283
	CTCATAGGGCACCA CCA	284

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
TAT-TGT Tyr-220 to Cys Li-Fraumeni syndrome	ATTGCGTGTGGAGTATTGGATGACAGAACACTTTGACA TAGTGTGGTGGTGCCTCATGAGCCGCCTGAGGTCCTGGTTG CAACTGGGTCTCTGGGAGGGAGGGTAAGGGTGGTT	285
	AACCACCCCTAACCCCTCCTCCCAGAGACCCCAGTTGCAAAC CAGACCTCAGGCCGCATAGGGCACCAACACTATGTCG AAAAGTGTTCGTCACTCAAATACTCCACACGCAAAT	286
	GGTGCCTCATGAGCCGC	287
	GCGGCTCATAGGGCAC	288
cTCT-ACT Ser-227 to Thr Rhabdomyosarcoma	CACAGGTCTCCCCAAGGCGCACTGGCCTCATCTGGCCTG TGTATCTCCTAGGTTGGCTCTGACTGTACCAACATCCACTAC AACTACATGTAAACAGTCCCTGCATGGCGGCATGA	289
	TCATGCCGCCATGCAGGAACGTGTTACACATGTAGTTGAGT GGATGGTGGTACAGTCAGAGCCAACCTAGGAGATAACACAG GCCCAAGATGAGGCCAGTGCGCCTGGGAGACCTGTG	290
	AGGTTGGCTCTGACTGT	291
	ACAGTCAGAGCCAACCT	292
cCAC-AAC His-233 to Asn Glioma	GCACTGGCCTCATCTGGCCTGTGTTATCTCCTAGGTTGGC TCTGACTGTACCAACCATCCACTACAACATACATGTAAACAGTT CCTGCATGGCGGCATGAACCGGAGGCCATCCTCA	293
	TGAGGATGGGCCTCCGGTTCATGCCGCCATGCAGGAACGTG TTACACATGTAGTTGAGTGGATGGTGGTACAGTCAGAGCCA ACCTAGGAGATAACACAGGCCAAGATGAGGCCAGTGC	294
	CCACCATCCACTACAAC	295
	GTTGTAGTGGATGGTGG	296
cAAC-GAC Asn-235 to Asp Adrenocortical carcinoma	GCCTCATCTGGCCTGTGTTATCTCCTAGGTTGGCTCTGAC TGTACCAACCATCCACTACAACATACATGTAAACAGTCCCTGCA TGGCGGCATGAACCGGAGGCCATCCTCACCATCA	297
	TGATGGTGGAGATGGCCTCCGGTTCATGCCGCCATGCAG GAACGTGTTACACATGTAGTTGAGTGGATGGTGGTACAGTC GAGCCAACCTAGGAGATAACACAGGCCAAGATGAGGC	298
	TCCACTACAACATACATG	299
	CATGTAGTTGAGTGGAA	300
AAC-AGC Asn-235 to Ser Rhabdomyosarcoma	CCTCATCTGGCCTGTGTTATCTCCTAGGTTGGCTCTGACT GTACCAACCATCCACTACAACATACATGTAAACAGTCCCTGCA GGCGGCATGAACCGGAGGCCATCCTCACCATCA	301

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGATGGTGAGGA <u>TGGGCCTCCGGTT</u> CATGCCGCCATGCA GGA <u>ACTGT</u> TACACATGTAG <u>TTG</u> TAGTGGATGGTGGTACAGTC AGAGCCAACCTAGGAGATAACACAGGCCAAGATGAGG	302
	CCACTACA <u>ACT</u> ACATGT	303
	ACATGTAG <u>TTG</u> TAGTGG	304
ATCc-ATG Ile-251 to Met Glioma	CATCCCACTACA <u>ACTACATGT</u> TAACAG <u>TTCC</u> TGCATGGCGG CATGAAC <u>CGGAGG</u> CCC <u>ATC</u> CTCACCATCATCAC <u>ACTGG</u> AAGA CTCCAGGT <u>CAGGAGCC</u> ACTGCCACC <u>CTGC</u> ACACTGG	305
	CCAGTGTGCAGGGTGG <u>CAAGTGG</u> C <u>TCTG</u> AC <u>CTGG</u> G <u>AGT</u> CTT CCAGTGT <u>GATG</u> T <u>GATGG</u> <u>TGAGG</u> <u>ATGG</u> C <u>CTCCGG</u> <u>TT</u> CATGCCG CC <u>ATGC</u> AG <u>GAAC</u> T <u>GTT</u> ACACATGTAG <u>TTG</u> TAG <u>GG</u> ATG	306
	AGGCC <u>CATC</u> CTCACCAT	307
	ATGGT <u>GAGG</u> <u>ATGG</u> C <u>CT</u>	308
ACA-ATA Thr-256 to Ile Glioblastoma	ACATGT <u>GT</u> AA <u>CAGT</u> CC <u>CTGC</u> ATGGCGG <u>CATG</u> A <u>ACCGG</u> <u>GAGG</u> CC <u>CATC</u> CT <u>ACC</u> AT <u>CATC</u> <u>AC</u> ACT <u>GGAA</u> G <u>ACTCC</u> <u>AGGT</u> C <u>AGGA</u> GCC <u>ACTT</u> GC <u>CCACC</u> CT <u>GC</u> AC <u>ACTGG</u> C <u>CTG</u> <u>CTG</u> T <u>GCCCC</u>	309
	TGGGGC <u>CACAGC</u> AG <u>GGCC</u> <u>AGTGT</u> G <u>CAGGG</u> T <u>GG</u> <u>CAAGTGG</u> <u>CTCC</u> TG <u>ACCTGG</u> <u>AGTCTT</u> <u>CCAGTGT</u> <u>GATG</u> T <u>GATGG</u> <u>GAGG</u> <u>ATGG</u> C <u>CT</u> CC <u>GGTT</u> CAT <u>GCCGCC</u> <u>CCATGC</u> AG <u>GAAC</u> T <u>GTT</u> ACACATGT	310
	CAT <u>CATC</u> <u>AC</u> ACT <u>GGAA</u> G	311
	CTTCC <u>AGTGT</u> <u>GATG</u>	312
CTG-CAG Leu-257 to Gln Li-Fraumeni syndrome	TGT <u>GT</u> AA <u>CAGT</u> CC <u>CTGC</u> ATGGCGG <u>CATG</u> A <u>ACCGG</u> <u>GAGG</u> CCC AT <u>CCTC</u> AC <u>CC</u> AT <u>CATC</u> <u>AC</u> ACT <u>GGAA</u> G <u>ACTCC</u> <u>AGGT</u> C <u>AGGAGC</u> ACT <u>GG</u> C <u>CCACC</u> CT <u>GC</u> AC <u>ACTGG</u> C <u>CTG</u> <u>CTG</u> T <u>GCCCC</u> <u>AGCC</u>	313
	GG <u>CTGGGG</u> <u>CACAGC</u> AG <u>GGCC</u> <u>AGTGT</u> G <u>CAGGG</u> T <u>GG</u> <u>CAAGTGG</u> CT <u>CCCTGAC</u> <u>CTGGAGT</u> <u>CTTCC</u> <u>AGTGT</u> <u>GATG</u> T <u>GATGG</u> <u>GAGG</u> <u>ATGG</u> GC <u>CTCCGG</u> <u>TT</u> CAT <u>GCCGCC</u> <u>CCATGC</u> AG <u>GAAC</u> T <u>GTT</u> ACACAC	314
	CAT <u>CAC</u> <u>AC</u> <u>GGAA</u> G <u>ACT</u>	315
	AGT <u>CTTCC</u> <u>AGTGT</u> <u>GATG</u>	316
10 CTG-CCG Leu-265 to Pro Li-Fraumeni syndrome	GAC <u>CTGATT</u> <u>CC</u> TT <u>ACTGC</u> CT <u>CTG</u> <u>CTCT</u> <u>CTT</u> <u>CC</u> T <u>ATC</u> CT GAG <u>TAGTGG</u> <u>TAAT</u> <u>CTACT</u> <u>GGGAC</u> <u>GGAAC</u> <u>AGC</u> <u>CTT</u> <u>GAGGT</u> <u>GCG</u> TG <u>TTTGTG</u> <u>CC</u> GT <u>CTGG</u> <u>AGGAC</u> <u>AGGC</u> <u>ACAAAC</u> <u>ACGC</u> <u>CAC</u> <u>AGAG</u>	317
	TCT <u>GTGCGCCGGT</u> <u>CTCTCC</u> <u>CAGGAC</u> <u>AGGC</u> <u>ACAAAC</u> <u>ACGC</u> <u>CAC</u> <u>AGAG</u> CT <u>CAAAGCTG</u> <u>TCG</u> <u>CTCC</u> <u>AGTAG</u> <u>ATTACCA</u> <u>CTAC</u> <u>TCA</u> <u>GGGAT</u> AG <u>AAAAGAGAAG</u> <u>CAAGAGG</u> <u>CAGTA</u> <u>AGGAA</u> <u>ATCAGG</u> <u>TC</u>	318

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAATCTACT <u>GGGACGGA</u>	319
	TCCGTCCC <u>A</u> GTAGATTAA	320
gCGT-TGT Arg-273 to Cys Li-Fraumeni syndrome	TGCTTCTCTTTCTATCCTGAGTAGTGGAATCTACTGGAC GGAACAGCTTGAGGTG <u>C</u> GTGTTGTGCCTGTCTGGAGA GACCGGCGCACAGAGGAAGAGAAATCTCCGCAAGAAAG	321
	CTTCTTGC <u>GGAGATTCTCTCTGTGCGCCGGTCTCTCC</u> CAGGACAGGCACAAACAC <u>G</u> CACCTCAAAGCTGTCCGTC GTAGATTACCACTACTCAGGATAGGAAAAGAGAAAGCA	322
	TTGAGGTG <u>C</u> GTGTTGT	323
	ACAAACAC <u>G</u> CACCTCAA	324
TGT-TAT Cys-275 to Tyr Li-Fraumeni syndrome	CTTTCTATCCTGAGTAGTGGAATCTACTGGACGGAACA GCTTGAGGTGCGTGT <u>TTGTGCCTGTCTGGAGAGACCGG</u> CGCACAGAGGAAGAGAAATCTCCGCAAGAAAGGGAGGCC	325
	GGCTCCCC <u>TTTCTTGC</u> GGAGATTCTCTCTGTGCGCCGG TCTCTCCAGGACAGGCACAAACACGCACCTCAAAGCTGTC CGTCCCAGTAGATTACCACTACTCAGGATAGGAAAAG	326
	GCGTGT <u>TTGTGCCTGTC</u>	327
	GACAGGCACAAACACGC	328
CCT-CTT Pro-278 to Leu Breast cancer	TCCTGAGTAGTGGAATCTACTGGACGGAACAGCTTGAGG TGC <u>GTGTTGTGCCTGTCTGGAGAGACCGGCGCACAGAG</u> GAAGAGAAATCTCCGCAAGAAAGGGAGCCTCACCAACGA	329
	TCGTGGT <u>GAGGCTCCCTTCTTGC</u> GGAGATTCTCTCTCT GTGCGCCGGTCTCTCC <u>A</u> GGACAGGCACAAACACGCACCTC AAAGCTGTTCCGTCCCAGTAGATTACCACTACTCAGGA	330
	TGCCTGTC <u>CTGGGAGAG</u>	331
	CTCTCCC <u>A</u> GGACAGGC	332
	GTAGTGGTAATCTACTGGACGGAACAGCTTGAGGTGCGTG TTTGTGCCTGTCTGGAGAGACCGGCGCACAGAGGAAGAG AATCTCCGCAAGAAAGGGAGCCTCACCAACGAGCTGCC	333
10 AGA-AAA Arg-280 to Lys Glioma	GGCAGCTCGTGGT <u>GAGGCTCCCTTCTTGC</u> GGAGATTCTCT TCCTCTGTGCGCCGGTCTCTCC <u>A</u> GGACAGGCACAAACACG CACCTCAAAGCTGTTCCGTCCCAGTAGATTACCACTAC	334
	TCCTGGG <u>A</u> GAGACCGGC	335
	GCCGGTCTCTCCCAGGA	336

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
GAA-GCA Glu-286 to Ala Adrenocortical carcinoma	GGAACAGCTTGAGGTGCGTGTGCTGCCTGGGAGA GACCAGCGCACAGAGGAAG <u>A</u> GAATCTCCGCAAGAAAGGGGA GCCTCACCAACGAGCTGCCGCCAGGGAGCACTAACGCGAGG	337
	CCTCGCTTAGTGCTCCCTGGGGCAGCTCGTGGTGAGGCTC CCCTTCTTGCAGGAGATT <u>T</u> CTTCCCTGTGCGCCGGTCTCT CCCAGGACAGGCACAAACACGGCACCTCAAAGCTGTTCC	338
	AGAGGAAG <u>A</u> GAATCTCC	339
	GGAGATTCTTCCCT	340
CGA-CCA Arg-306 to Pro Rhabdomyosarcoma	AAGAGAAATCTCCGCAAGAAAGGGGAGCCTCACACGAGCTG CCCCCAGGGAGCACTAAC <u>G</u> GAGGTAAGCAAGCAGGACAAGA AGCGGTGGAGGAGACCAAGGGTGCAGTTATGCCTCAGAT	341
	ATCTGAGGCATAACTGCACCCCTGGTCTCCTCCACCGCTTCT TGTCTGCTTGC <u>T</u> ACCTCGCTTAGTGCTCCCTGGGGCAGC TCGTGGTGAGGCTCCCTTCTTGC <u>G</u> GAGATTCTCTT	342
	CACTAAC <u>G</u> GAGGTAAGC	343
	GCTTACCTCGCTTAGTG	344
gCGA-TGA Arg-306 to Term Li-Fraumeni syndrome	GAAGAGAAATCTCCGCAAGAAAGGGGAGCCTCACACGAGCT GCCCCCAGGGAGCACTAAC <u>G</u> GAGGTAAGCAAGCAGGACAAG AAGCGGTGGAGGAGACCAAGGGTGCAGTTATGCCTCAGA	345
	TCTGAGGCATAACTGCACCCCTGGTCTCCTCCACCGCTTCTT GTCCTGCTTGC <u>T</u> ACCTCGCTTAGTGCTCCCTGGGGCAGCT CGTGGTGAGGCTCCCTTCTTGC <u>G</u> GAGATTCTCTT	346
	GCACTAAC <u>G</u> GAGGTAAG	347
	CTTACCTCGCTTAGTG	348
gCGC-TGC Arg-337 to Cys Osteosarcoma	GGTACTGTGAATATA <u>T</u> ACTTACTCTCCCTCCTGTGCTGC AGATCCGTGGCGTGAG <u>C</u> GCTTCGAGATGTTCCGAGAGCTG AATGAGGCCTTGA <u>A</u> CTCAAGGATGCCAGGCTGGGA	349
	TCCCAGCCTGGCATCCTGAGTTCAAGGCCTCATT <u>C</u> AGCT CTCGGAACATCTCGAAG <u>C</u> GCTCACGCCACGGATCTGCAGC AACAGAGGAGGGGGAGAAGTAAGTATATTACAGTACC	350
	GGCGTGAG <u>C</u> GCTTCGAG	351
	CTCGAAC <u>G</u> GCTCACGCC	352
CTG-CCG Leu-344 to Pro Li-Fraumeni syndrome	CTCCCCCTCCTGTGCTGCAGATCCGTGGCGTGAGCGC TTCGAGATGTTCCGAGAGCTGAATGAGGCCTGGAACTCAAG GATGCCAGGCTGGAAAGGAGCCAGGGGGAGCAGGGC	353

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCCTGCTCCCCCTGGCTCCTCCCAGCCTGGGCATCCTT GAGTTCCAAGGCCTCATTCA <u>G</u> CTCTCGAACATCTGAAGCG CTCACGCCACGGATCTGCAGAACAGAGGAGGGGGAG	354
	CCGAGAG <u>G</u> TGAATGAGG	355
	CCTCATT <u>C</u> AGCTCTCGG	356

EXAMPLE 6
beta globin

Hemoglobin, the major protein in the red blood cell, binds oxygen reversibly and is responsible for the cells' capacity to transport oxygen to the tissues. In adults, the major hemoglobin is hemoglobin A, a tetrameric protein consisting of two identical alpha globin chains and two beta globin chains. Disorders involving hemoglobin are among the most common genetic disorders worldwide, with approximately 5% of the world's population being carriers for clinically important hemoglobin mutations. Approximately 300,000 severely affected homozygotes or compound heterozygotes are born each year.

Mutation of the glutamic acid at position 7 in beta globin to valine causes sickle cell anemia, the clinical manifestations of which are well known. Mutations that cause absence of beta chain cause beta-zero-thalassemia. Reduced amounts of detectable beta globin causes beta-plus-thalassemia. For clinical purposes, beta-thalassemia is divided into thalassemia major (transfusion dependent), thalassemia intermedia (of intermediate severity), and thalassemia minor (asymptomatic). Patients with thalassemia major present in the first year of life with severe anemia; they are unable to maintain a hemoglobin level about 5 gm/dl.

The beta-thalassemias were among the first human genetic diseases to be examined by means of recombinant DNA analysis. Baysal et al., *Hemoglobin* 19(3-4):213-36 (1995) and others provide a compendium of mutations that result in beta-thalassemia.

Hemoglobin disorders were among the first to be considered for gene therapy. Transcriptional silencing of genes transferred into hematopoietic stem cells, however, poses one of the most significant challenges to its success. If the transferred gene is not completely silenced, a progressive decline in gene expression is often observed. Position effect variegation (PEV) and silencing mechanisms may act on a transferred globin gene residing in chromatin outside of the normal globin locus during the important terminal phases of erythroblast development when globin transcripts normally

accumulate rapidly despite heterochromatization and shutdown of the rest of the genome. The attached table discloses the correcting oligonucleotide base sequences for the beta globin oligonucleotides of the invention.

Table 12
Beta Globin Mutations and Genome-Correcting Oligos

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Sequence 5' to 3' direction

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Sickle Cell Anemia GLU-7-VAL GAG to GTG	TCTGACACAACGTGTTCACTAGCAACCTCAAACAGACACCA TGGTGCACCTGACTCCTG <u>A</u> GGGAGAAGTCTGCCGTTACTGCC CTGTGGGGCAAGGTGAACGTGGATGAAGTTGGTGGTGA	357
	TCACCACCAACACTCATCCACGTTCACCTGCCAACAGGGCA GTAACGGCAGACTCTCCT <u>C</u> AGGAGTCAGGTGCACCATGGT GTCTGTTGAGGTTGCTAGTGAACACAGTTGTGTCAGA	358
	GA <u>T</u> CCCT <u>G</u> AGGAGAAGT	359
	ACTTCT <u>C</u> TCAGGAGTC	360
Thalassaemia Beta MET-0-ARG ATG to AGG	CTATTGCTTACATTGCTTCTGACACAACGTGTTCACTAGCA ACCTCAAACAGACACC <u>A</u> GGTGACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	361
	ACGTTCACCTGCCAACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACC <u>A</u> GGTGTCTGTTGAGGTTGCT AGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATA	362
	AGACACC <u>A</u> GGTGCACC	363
	GGTGCACC <u>A</u> GGTGTCT	364
	TATTGCTTACATTGCTTCTGACACAACGTGTTCACTAGCAA CCTCAAACAGACACC <u>A</u> GGTGACCTGACTCCTGAGGAGAA GTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTG	365
Thalassaemia Beta MET-0-ILE ATG to ATA	CACGTTCACCTGCCAACAGGGCAGTAACGGCAGACTTCT CCTCAGGAGTCAGGTGCACC <u>A</u> GGTGTCTGTTGAGGTTGC TAGTGAACACAGTTGTGTCAGAAGCAAATGTAAGCAATA	366
	GACACC <u>A</u> GGTGCACCT	367
	AGGTGCACC <u>A</u> GGTGTGTC	368
	TATTGCTTACATTGCTTCTGACACAACGTGTTCACTAGCAA CCTCAAACAGACACC <u>A</u> GGTGACCTGACTCCTGAGGAGAA GTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTG	369

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CACGTTCACCTGCCAACAGGGCAGTAACGGCAGACTTCT CCTCAGGAGTCAGGTGCACC <u>A</u> GGTGTCTGTTGAGGTTGC TAGTGAACACAGTTGTGTCAAAGCAAATGTAAGCAATA	370
	GACACC <u>A</u> GGTGCACCT	371
	AGGTGCACC <u>A</u> GGTGTC	372
Thalassaemia Beta MET-0-LYS ATG to AAG	CTATTGCTTACATTGCTTCTGACACA <u>A</u> CTGTGTTCACTAGCA ACCTCAAACAGACACC <u>A</u> GGTGCACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	373
	ACGTTCACCTGCCAACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACC <u>A</u> GGTGTCTGTTGAGGTTGCT AGTGAACACAGTTGTGTCAAAGCAAATGTAAGCAATAG	374
	AGACACC <u>A</u> GGTGCACC	375
	GGTGCACC <u>A</u> GGTGTC	376
Thalassaemia Beta MET-0-THR ATG to ACG	CTATTGCTTACATTGCTTCTGACACA <u>A</u> CTGTGTTCACTAGCA ACCTCAAACAGACACC <u>A</u> GGTGCACCTGACTCCTGAGGAGA AGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	377
	ACGTTCACCTGCCAACAGGGCAGTAACGGCAGACTTCTC CTCAGGAGTCAGGTGCACC <u>A</u> GGTGTCTGTTGAGGTTGCT AGTGAACACAGTTGTGTCAAAGCAAATGTAAGCAATAG	378
	AGACACC <u>A</u> GGTGCACC	379
	GGTGCACC <u>A</u> GGTGTC	380
Thalassaemia Beta MET-0-VAL ATG to GTG	TCTATTGCTTACATTGCTTCTGACACA <u>A</u> CTGTGTTCACTAGC AACCTCAAACAGACACC <u>A</u> GGTGCACCTGACTCCTGAGGAG AAGTCTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGT	381
	CGTTCACCTGCCAACAGGGCAGTAACGGCAGACTTCTCC TCAGGAGTCAGGTGCACC <u>A</u> GGTGTCTGTTGAGGTTGCTAG TGAACACAGTTGTGTCAAAGCAAATGTAAGCAATAGA	382
	CAGACACC <u>A</u> GGTGCAC	383
	GTGCACC <u>A</u> GGTGTC	384
Thalassaemia Beta TRP-16-Term TGG to TGA	TCAAACAGACACC <u>A</u> GGTGCACCTGACTCCTGAGGAGAA <u>G</u> T CTGCCGTTACTGCCCTGTGGGGCAAGGTGAACGTGGATGAA GTTGGTGGTGA <u>G</u> GGCCCTGGCAGGTTGGTATCAAGGTAA	385
	TAACCTGATACCAACCTGCCAACGGGCTCACCACCAACTTC ATCCACGTTCACCTGCC <u>C</u> ACAGGGCAGTAACGGCAGACT TCTCCTCAGGAGTCAGGTGCACC <u>A</u> GGTGTCTGTTGA	386

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCCTGT <u>GGGG</u> CAAGGT	387
	ACCTTGCCCCACAGGGC	388
Thalassaemia Beta TRP-16-Term TGG to TAG	CTCAAACAGACACCATGGTGACCTGACTCCTGAGGAGAAG TCTGCCGTTACTGCCCTGT <u>GGGG</u> CAAGGTGAACGTGGATGA AGTTGGTGGTGAGGCCCTGGGCAGGTTGGTATCAAGGTT	389
	AACCTTGATACCAACCTGCCCA <u>GGGC</u> CTCACCAACTCA TCCACGTTCACCTGCC <u>CC</u> ACAGGGCAGTAACGGCAGACTT CTCCTCAGGAGTCAGGTGCACCATGGTGTCTGTTGAG	390
	TGCCCTGT <u>GGGG</u> CAAGG	391
	CCTTGCCCCACAGGGC	392
Thalassaemia Beta LYS-18-Term AAG to TAG	ACAGACACC <u>ATGGTGACCTGACTCCTGAGGAGAAGTCTGC</u> CGTTACTGCCCTGT <u>GGGG</u> CAAGGTGAACGTGGATGAAGTTG GTGGTGAGGCCCTGGCAGGTTGGTATCAAGGTTACAAG	393
	CTTGTAA <u>CC</u> TGATACCAACCTGCCCA <u>GGGC</u> CTCACCAAA CTTCATCCACGTTCACCT <u>GGGG</u> CAAGGGCAGTAACGGCA GACTTCTCCTCAGGAGTCAGGTGCACCATGGTGTCTGT	394
	TGTGGGG <u>CAAGGT</u> GAAC	395
	GTTCACCT <u>GGGG</u> CACA	396
Thalassaemia Beta ASN-20-SER AAC to AGC	CCATGGTGACCTGACTCCTGAGGAGAAGTCTGCCGTTACT GCCCTGT <u>GGGG</u> CAAGGTGA <u>ACGTGGAT</u> GAAGTTGGTGGTGA GCCCTGGCAGGTTGGTATCAAGGTTACAAGACAGGTT	397
	AACCTGTCTTGTAACCTTGATACCAACCTGCCCA <u>GGGC</u> CTCA CCACCAACTTCATCCACG <u>TT</u> CACCTTGCCCCACAGGGCAGTA ACGGCAGACTTCTCCTCAGGAGTCAGGTGCACCATGG	398
	CAAGGTGA <u>ACGTGGAT</u> G	399
	CATCCACG <u>TT</u> CACCTTG	400
10 Thalassaemia Beta GLU-23-ALA GAA to GCA	ACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCCCTGTGG GGCAAGGTGAACGTGGAT <u>GAAGTTGGTGGT</u> GAGGCCCTGG GCAGGTTGGTATCAAGGTTACAAGACAGGTTAAGGAGAC	401
	GTCTCCTTAAACCTGTCTGTAACCTGATACCAACCTGCC AGGGCCTCACCACCAACT <u>TCATCCACGTT</u> CACCTTGCCCCAC AGGGCAGTAACGGCAGACTTCTCCTCAGGAGTCAGGT	402
	CGTGGAT <u>GAAGTTGGT</u> G	403
	CACCAACT <u>TCATCCACG</u>	404

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta GLU-23-term GAA to TAA	CACCTGACTCCTGAGGAGAAGTCTGCCGTTACTGCCCTGTG GGGCAAGGTGAACGTGGAT <u>GAAGTTGGTGGT</u> GAGGCCCTG GGCAGGTTGGTATCAAGGTTACAAGACAGGTTAAGGAGA	405
	TCTCCTTAAACCTGCTTGTAAACCTGATACCAACCTGCCCA GGGCCTCACCAAC <u>TTCATCCACGTT</u> CACCTGCCCA GGGCAGTAACGGCAGACTTCCTCAGGAGTCAGGTG	406
	ACGTGGAT <u>GAAGTTGGT</u>	407
	ACCAACTT <u>CATCCACGT</u>	408
Thalassaemia Beta GLU-27-LYS GAG to AAG	GAGGAGAAGACTGCTGCAATGCCCTGTGGGGCAAAGTGAA CGTGGATGCAGTTGGTGGT <u>GAGGCCCTGGG</u> CAGGTTGGTAT CAAGGTTATAAGAGAGGGCTCAAGGAGGCAAATGGAAACT	409
	AGTTCCATTGCTCCTTGAGCCTCTCTTATAACCTTGATAC CAACCTGCCCA <u>GGGCCTCAC</u> CCACCAACTGCATCCACGTTCA CTTGCCCCACAGGGCATTGACAGCAGTCTTCCTC	410
	TTGGTGGT <u>GAGGCCCTG</u>	411
	CAGGGCCT <u>CACCACCAA</u>	412
Thalassaemia Beta GLU-27-Term GAG to TAG	GAGGAGAAGACTGCTGCAATGCCCTGTGGGGCAAAGTGAA CGTGGATGCAGTTGGTGGT <u>GAGGCCCTGGG</u> CAGGTTGGTAT CAAGGTTATAAGAGAGGGCTCAAGGAGGCAAATGGAAACT	413
	AGTTCCATTGCTCCTTGAGCCTCTCTTATAACCTTGATAC CAACCTGCCCA <u>GGGCCTCAC</u> CCACCAACTGCATCCACGTTCA CTTGCCCCACAGGGCATTGACAGCAGTCTTCCTC	414
	TTGGTGGT <u>GAGGCCCTG</u>	415
	CAGGGCCT <u>CACCACCAA</u>	416
Thalassaemia Beta ALA-28-SER GCC to TCC	GAGAAGACTGCTGCAATGCCCTGTGGGGCAAAGTGACGT GGATGCAGTTGGTGGT <u>GAGGCCCTGGG</u> CAGGTTGGTATCAA GGTTATAAGAGAGGGCTCAAGGAGGCAAATGGAAACTGGG	417
	CCCAGTTCCATTGCTCCTTGAGCCTCTCTTATAACCTGATAC TACCAACCTGCCCA <u>GGGCCTCAC</u> CCACCAACTGCATCCACGTT TCACCTTGCCCCACAGGGCATTGACAGCAGTCTTC	418
	GTGGTGAG <u>GGGCCCTGGG</u> C	419
	GCCCAGGGCCTCACCAAC	420

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta ARG-31-THR AGG to ACG	CTGTCAATGCCCTGGGGCAAAGTGAACGTGGATGCAGTT GGTGGTGAGGCCCTGGC <u>A</u> GGTTGGTATCAAGGTTATAAGA GAGGCTCAAGGAGGCAAATGGAAACTGGGCATGTGAGA	421
	TCTACACATGCCAGTTCCATTGCCCTCCTGAGCCTCTT ATAAACCTGATACCAAC <u>C</u> TGCCAGGGCCTCACCAACTG CATCCACGTTCACTTGCCCCACAGGGCATTGACAG	422
	CCTGGC <u>A</u> GGTTGGTAT	423
	ATACCAAC <u>C</u> TGCCAGG	424
Thalassaemia Beta Leu-33-GLN CTG to CAG	TGGGTTCTGATAGGCACTGACTCTCTGTCCTGGGCTGTT TTCCTACCC <u>C</u> TCAGATT <u>A</u> CTGGTGGT <u>C</u> ACCC <u>C</u> TTGGACCCAGA GGTTCTTGAGTCCTTGGGATCTGCTCTCCTGA	425
	TCAGGAGAGGACAGATCCCCAAAGGACTCAAAGAAC <u>C</u> CTG GGTCCAAGGGTAGACC <u>A</u> CTGAGGGTAGGAAAAC AGCCC <u>A</u> AGGGACAGAGAGTCAGTGCCTATCAGAAACCC	426
	CAGATT <u>A</u> CTGGTGGTCT	427
	AGACCACC <u>A</u> GTAA <u>C</u> TG	428
Thalassaemia Beta TYR-36-Term TAC to TAA	ATAGGCACTGACTCTCTGTCCTGGGCTGTTCTACCC CAGATT <u>A</u> CTGGTGGT <u>C</u> AC <u>C</u> CTGGACCCAGAGGTTCTTG GTC <u>C</u> TTGGGATCTGCTCTCCTGATGCTGTTATG	429
	CATAACACGATCAGGAGAGGACAGATCCCCAAAGGACTCAA GAAC <u>C</u> CTCTGGGT <u>C</u> CAAGGGTAGACC <u>A</u> CTGAGGG TAGGAAAACAGCCC <u>A</u> AGGGACAGAGAGTCAGTGCCTAT	430
	GTGGT <u>C</u> AC <u>C</u> CTGGAC	431
	GTCCAAGGGTAGACCAC	432
Thalassaemia Beta TRP-38-Term TGG to TGA	ACTGACTCTCTGTCCTGGGCTGTTCTACCC <u>C</u> AGATT ACTGGTGGT <u>C</u> AC <u>C</u> CTGG <u>A</u> CC <u>C</u> AGAGGTTCTTGAGTCCT TGGGGATCTGCTCTCCTGATGCTGTTATGGCAAC	433
	GTTGCCATAACAGCATCAGGAGAGGACAGATCCCCAAAGG ACTCAAAGAAC <u>C</u> CTGGGT <u>C</u> CAAGGGTAGACC <u>A</u> CTGAGGT TAGGGTAGGAAAACAGCCC <u>A</u> AGGGACAGAGAGTCAGT	434
	TAC <u>C</u> CTGG <u>G</u> ACCCAGAG	435
	CTCTGGGT <u>C</u> CAAGGGTA	436
Thalassaemia Beta TRP-38-Term TGG to TAG	CACTGACTCTCTGTCCTGGGCTGTTCTACCC <u>C</u> AGAT TA <u>C</u> CTGGTGGT <u>C</u> AC <u>C</u> CTGG <u>A</u> CC <u>C</u> AGAGGTTCTTGAGTCCT TGGGGATCTGCTCTCCTGATGCTGTTATGGCAAC	437

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTGCCCATAACAGCATCAGGAGAGGACAGATCCCCAAAGGA CTCAAAGAACCTCTGGTCCAAGGGTAGACCACAGTAATCT GAGGGTAGGAAAACAGCCCAGGGACAGAGAGTCAGTG	438
	CTACCCT <u>TG</u> GACCCAGA	439
	TCTGGTCCAAGGGTAG	440
Thalassaemia Beta GLN-40-Term CAG-TAG	ACTCTCTGCCCCTGGCTTTCTACCCCTCAGATTACTG GTGGTCTACCCCTGGACCC <u>A</u> GAGGTTCTTGAGTCCTTGGG GATCTGTCTCTCCTGATGCTGTTATGGCAACCCCTA	441
	TAGGGTTGCCATAACAGCATCAGGAGAGGACAGATCCCCA AAGGACTCAAAGAACCTCT <u>G</u> GGTCCAAGGGTAGACCACAG TAATCTGAGGGTAGGAAAACAGCCCAGGGACAGAGAGT	442
	CTTGGACCC <u>A</u> GAGGTTC	443
	GAACCTCT <u>G</u> GGTCCAAG	444
Thalassaemia Beta GLU-44-Term GAG to TAG	TTGGGCTGTTTCTACCCCTCAGATTACTGGTGGTCTACCCCT TGGACCCAGAGGTTCTT <u>G</u> AGTCCTTGGGATCTGTCCTCT CCTGATGCTGTTATGGCAACCCCTAAGGTGAAGGCTC	445
	GAGCCTCACCTAGGGTCCCATAACAGCATCAGGAGAG GACAGATCCCCAAAGGACTCAAAGAACCTCTGGTCCAAGG GTAGACCACCAAGTAATCTGAGGGTAGGAAAACAGCCC	446
	GGTTCTT <u>G</u> AGTCCTT	447
	AAAGGACTCAAAGAAC	448
Thalassaemia Beta LYS-62-Term AAG to TAG	TTCTTGAGTCCTTGGGATCTGTCCTCTCCTGATGCTGTTA TGGCAACCCCTAAGGT <u>G</u> AGGCTCATGGCAAGAAGGTGCTA GGTGCCTTAGTGTGATGGCCTGGCTCACCTGGACAACC	449
	GGTTGTCCAGGTGAGCCAGGCCATCACTAAAGGCACCTAGC ACCTTCTGCCATGAGCCT <u>T</u> CACCTAGGGTGGCCATAACA GCATCAGGAGAGGACAGATCCCCAAAGGACTCAAAGAA	450
	CTAAGGT <u>G</u> AGGCTCAT	451
	ATGAGCCT <u>T</u> CACCTTAG	452
Thalassaemia Beta SER-73-ARG AGT to AGA	TGCTGTTATGGCAACCCCTAAGGTGAAGGCTCATGGCAAGA AGGTGCTAGGTGCCTTAGTGTGATGGCCTGGCTCACCTGGAC AACCTCAAGGGCACTTTCTCAGCTGAGTGAGCTGCAC	453
	GTGCAGCTCACTCAGCTGAGAAAAAGTGCCTTGAGGTTGTC CAGGTGAGCCAGGCCAT <u>C</u> ACTAAAGGCACCTAGCACCTCT TGCCATGAGCCTCACCTAGGGTGGCCATAACAGCA	454

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCCTTAG <u>T</u> GATGGCCT	455
	AGGCCAT <u>CA</u> CTAAAGGC	456
Haemolytic Anaemia GLY-75-VAL GGC to GTC	TTATGGGCAACCCTAAGGTGAAGGCTCATGGCAAGAAGGTG CTAGGTGCCTTAGT <u>GATGGCCTGGCTCACCTGGACAAACCT</u> CAAGGGCACTTTCTCAGCTGAGTGACTGACTGTGA	457
	TCACAGTGCAGCTCACTCAGCTGAGAAAAAGTGCCCTGAG GTTGTCCAGGTGAG <u>CCAGGC</u> CATCACTAAAGGCACCTAGCA CCTCTGCCATGAGCCTCACCTAGGGTTGCCATAA	458
	TAGTGAT <u>GGCCTGGCT</u>	459
	GAGCCAG <u>GGCC</u> CATCACTA	460
Thalassaemia Beta GLU-91-Term GAG to TAG	GCCTTAGT <u>GATGGCCTGGCTCACCTGGACAAACCTCAAGGG</u> CACCTTGCCACACTGAGT <u>GAGCTG</u> ACTGTGACAAGCTGC ACGTGGATCCTGAGAAC <u>TTCAGGGTGAGTCTATGGGACC</u>	461
	GGTCCC <u>CATAGACTCAC</u> CCCTGAAGTTCTCAGGATCCACGTGCA GCTTGT <u>CACAGTGCAGCT</u> ACTCAGTGTGGCAAAGGTGCC TTGAGGTTGTCCAGGTGAGCCAGGCCATCACTAAAGGC	462
	CACTGAGT <u>GAGCTGCAC</u>	463
	GTGCAG <u>GCTCA</u> TCAGT	464
Thalassaemia Beta VAL-99-MET GTG to ATG	CTGGACAACCTCAAGGGACTTTCTCAGCTGAGTGAGCTG CACTGTGACAAG <u>CTGCAC</u> GTGGATCCTGAGAAC <u>TTCAGGGT</u> GAGTCCAGGAGATGCTTCACTTTCTCTTTACTTT	465
	GAAAGTAAAAGAGAAAAGTGAAGCATCTCCTGGACTCACCC TGAAGTTCTCAGGATCC <u>ACGTG</u> CAGCTGTCA <u>AGTGCAGCT</u> CACTCAGCTGAGAAAAGTGCCCTGAGGTGTCCAG	466
	AGCTGCAC <u>GTGGATCCT</u>	467
	AGGATCC <u>ACGTG</u> CAGCT	468
Thalassaemia Beta LEU-111-PRO CTG-CCG	CCCTTTGCTAATCATGTT <u>CATAC</u> CTTATCTTCCCTCCACA GCTCCTGGCAACGTG <u>C</u> GGTCTGTGCTGGCCCATCACT TTGGCAAAGAATT <u>CACCCC</u> ACCA <u>CGTGCAGGCTGCCTA</u>	469
	TAGGCAGCCTGCACTGGTGGGTGAATT <u>CTTGCCAAAGTG</u> ATGGGCCAGCACACAGACC <u>AGC</u> ACGTTGCCAGGAGCTGTG GGAGGAAGATAAGAGGTATGAACATGATTAGCAAAGGG	470
	CAACGTG <u>C</u> GGTCTGTG	471
	CACAGACC <u>AGC</u> ACGTTG	472

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Thalassaemia Beta CYS-113-Term TGT to TGA	GCTAATCATGTTACACCTTATCTTCCTCCACAGCTCCTGG GGCAACGTGCTGGTCTG <u>T</u> GTGCTGCCCATCACTTGGCAA AGAATTCCCCACCAGTGCAGGCTGCCTATCAGAAA	473
	TTTCTGATAGGCAGCCTGCACTGGTGGGTGAATTCTTGCC AAAGTGA <u>T</u> GGGCCAGCAC <u>A</u> CAGACCAGCACGTTGCCAGGA GCTGTGGAGGAAGATAAGAGGTATGAACATGATTAGC	474
	CTGGTCTG <u>T</u> GTGCTGGC	475
	GCCAGCAC <u>A</u> CAGACCAG	476
Thalassaemia Beta LEU-115-PRO CTG to CCG	TCATGTTACACCTTATCTTCCTCCACAGCTCCTGGCA ACGTGCTGGTCTGTG <u>T</u> GGCCCATCACTTGGCAAAGAAT TCACCCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGT	477
	ACCACTTCTGATAGGCAGCCTGCACTGGTGGGTGAATTCT TTGCCAAAGTGA <u>T</u> GGCC <u>A</u> GCACACAGACCAGCACGTTGCC CAGGAGCTGTGGAGGAAGATAAGAGGTATGAACATGA	478
	CTGTG <u>T</u> GCTGGCCCATC	479
	GATGGGCC <u>A</u> GCACACAG	480
Thalassaemia Beta ALA-116-ASP GCC to GAC	TGTTCATACCTTATCTTCCTCCACAGCTCCTGGCAACG TGCTGGTCTGTGCTGG <u>C</u> CATCACTTGGCAAAGAATTCA CCCCACCAGTGCAGGCTGCCTATCAGAAAGTGGTGGC	481
	GCCACCACTTCTGATAGGCAGCCTGCACTGGTGGGTGAA TTCTTGCCAAAGTGA <u>T</u> GGCC <u>A</u> GCACACAGACCAGCACGTT GCCAGGAGCTGTGGAGGAAGATAAGAGGTATGAACA	482
	TGTGCTGG <u>C</u> CATCACT	483
	AGTGATGG <u>C</u> CAGCACA	484
Thalassaemia Beta GLU-122-Term GAA to TAA	TTCCTCCCACAGCTCCTGGCAACGTGCTGGTCTGTGCT GGCCCATCACTTGGCAAAG <u>A</u> ATTCAACCCCCACCAGTGCAGG CTGCCTATCAGAAAGTGGTGGCTGGTGTGGCTAATGCC	485
	GGGCATTAGCCACACCAGCCACC <u>A</u> CTTCTGATAGGCAGCC TGC <u>A</u> CTGGTGGGTGAATT <u>T</u> TTGCCAAAGTGA <u>T</u> GGCCAG CACACAGACCAGCACGTTGCCAGGAGCTGTGGAGGA	486
	TTGGCAA <u>A</u> GAATT <u>C</u> ACC	487
	GGTGAATT <u>C</u> TTGCCAA	488
Thalassaemia Beta GLN-128-PRO CAG to CCG	GCAACGTGCTGGTCTGTGCTGGCCCATCACTTGGCAA GAATTCAACCCCCACCAGTGC <u>A</u> GGCTGCCTATCAGAAAGTGGT GGCTGGTGTGGCTAATGCCCTGGCCCACAAGTATCACTA	489

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAGTGATACTTGTGGGCCAGGGCATTAGCCACACACCAGCCAC CACTTCTGATAGGCAGCCT <u>G</u> CACTGGTGGGTGAATTCTTT GCCAAAGTGTAGGGCCAGCACACAGACCAGCACGTTGC	490
	ACCAAGTGC <u>A</u> GGCTGCCT	491
	AGGCAGCCT <u>G</u> CACTGGT	492
Thalassaemia Beta GLN-128-Term CAG to TAG	GGCAACGTGCTGGTCTGTGTGCTGGCCCACACTTGGCAA AGAATTCCCCCACCAGTGC <u>A</u> GGCTGCCTATCAGAAAGTGGT GGCTGGTGTGGCTAACGCCCTGGCCCACAAGTATCACT	493
	AGTGATACTTGTGGGCCAGGGCATTAGCCACACACCAGCCACC ACTTTCTGATAGGCAGCCT <u>G</u> CACTGGTGGGTGAATTCTTG CCAAAGTGTAGGGCCAGCACACAGACCAGCACGTTGCC	494
	CACCAAGTGC <u>A</u> GGCTGCC	495
	GGCAGCCT <u>G</u> CACTGGT	496
Thalassaemia Beta GLN-132-LYS CAG to AAG	GTCTGTGTGCTGGCCCACACTTGGCAAAGAATTACCCCCA CCAGTG <u>C</u> AGGCTGCCTAT <u>C</u> AGAAAGTGGTGGCTGGTGTGGC TAATGCCCTGGCCCACAAGTATCACTAAGCTCGCTTC	497
	GAAAGCGAGCTTAGTGATACTTGTGGGCCAGGGCATTAGCC ACACCAGCCACCACCTTCT <u>G</u> ATAGGCAGCCTGC <u>A</u> CTGGTGG GGTGAATTCTTGCCAAAGTGTAGGGCCAGCACACAGAC	498
	CTGCCTAT <u>C</u> AGAAAGTG	499
	CACTTCTGATAGGCAG	500

EXAMPLE 7
Retinoblastoma

10 Retinoblastoma (RB) is an embryonic neoplasm of retinal origin. It almost always presents in early childhood and is often bilateral. The risk of osteogenic sarcoma is increased 500-fold in bilateral retinoblastoma patients, the bone malignancy being at sites removed from those exposed to radiation treatment of the eye tumor.

15 The retinoblastoma susceptibility gene (pRB; pRb) plays a pivotal role in the regulation of the cell cycle. pRB restrains cell cycle progression by maintaining a checkpoint in late G₁ that controls commitment of cells to enter S phase. The critical role that pRB plays in cell cycle regulation explains its

status as archetypal tumor suppressor: loss of pRB function results in an inability to maintain control of the G₁ checkpoint; unchecked progression through the cell cycle is, in turn, a hallmark of neoplasia.

Blanquet et al., *Hum. Molec. Genet.* 4: 383-388 (1995) performed a mutation survey of the RB1 gene in 232 patients with hereditary or nonhereditary retinoblastoma. They systematically explored all 27 exons and flanking sequences, as well as the promoter. All types of point mutations were represented and found to be unequally distributed along the RB1 gene sequence. In the population studied, exons 3, 8, 18, and 19 were preferentially altered. The attached table discloses the correcting oligonucleotide base sequences for the retinoblastoma oligonucleotides of the invention.

Table 13
pRB Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Trp99Term TGG-TAG	AATATTGATCTTATTTTGTTCCCAGGGAGGTTATTCAA AAGAAAAAGGA <u>ACTGTGGGAATCTGTATCTTATTGCAGCA</u> GTTGACCTAGATGAGATGTCGTTCACTTTACTGA	501
	TCAGTAAA <u>AGTGAACGACATCTCATCTAGGTCAACTGCTGCA</u> ATAAAGATACAGATTCCCC <u>CACAGTTCC</u> TTTTCTTTGAATATA ACCTCCCTGGGAACAAAAAATAAGATCAAATATT	502
	GGA <u>ACTGTGGGAATCT</u>	503
	AGATTCCCC <u>CACAGTTCC</u>	504
Retinoblastoma Glu137Asp GAA-GAT	ATTTACTTTCTATTCTTCC <u>TTGTAGTGTCCATAAATTCTT</u> TAAC <u>TTACTAAAAGAAATTGATACCAGTACCAAGTTGATAAT</u> GCTATGTCAAGACTGTTGAAGAAGTATGATGTA	505
	TACATCAT <u>ACTTCTCAACAGTCTTGACATAGCATTATCAACTT</u> TGGTACTGGTATCA <u>ATTCTTTAGTAAGTAAAGAATTATGG</u> ACACTACAAAGGAAAGAATAGAAAAAGTAAAT	506
	CTAAA <u>AGAAATTGATAC</u>	507
	GTATCA <u>ATTCTTTAG</u>	508
Retinoblastoma Glu137Term GAA-TAA	TGATT <u>TACTTTCTATTCTTCC</u> TTGTAGTGTCCATAAATT CTTAA <u>CTTACTAAAAGAAATTGATACCAGTACCAAGTTGAT</u> AATGCTATGT <u>CAAGACTGTTGAAGAAGTATGATG</u>	509

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CATCATACTTCTTCAACAGTCTTGACATAGCATTATCAACTTT GGTACTGGTATCAATTCTTTAGTAAGTTAAGAATTATGG ACACTACAAAGGAAAGAATAGAAAAAGTAAATCA	510
	TACTAAA <u>GAAATTGAT</u>	511
	ATCAATT <u>CTTTAGTA</u>	512
Retinoblastoma Gln176Term CAA-TAA	AAAATGTTAAAAAGTCATAATGTTTCTTCAGGACATGTGA ACTTATATATTGAC <u>ACAACCCAGCAGTCGTAAGTAGTCAC</u> AGAATGTTATTTC <u>ACTTAAAAAAAAGATT</u> TT	513
	AAAATCTTTTTTTAAGTGA AAAATAACATTCTGTGAACTACT TACGA <u>ACTGCTGGTTGTGTCAAATATAAGTCACATGTCC</u> TGAAAAGAAAAACATTATGACTTTAACATTT	514
	ATTGAC <u>ACAACCCAGC</u>	515
	GCTGGGTT <u>GTGTCAAAT</u>	516
Retinoblastoma Ile185Thr ATA-ACA	TGATACATTTCCTGTTTTCTGCTTCTATTGTTAATA GGATATCTACTGAA <u>ATAAAATTCTGCATTGGTGCTAAAGTTTC</u> TTGGATCACATTATTAGCTAAAGGTAAGTT	517
	AACTTACCTTAGCTAATAAAATGTGATCCAAGAAACTTTA GCACCAATGCAGAA <u>TTTCAAGTAGATATCCTATTAAACAA</u> ATAGAAAGCAGAAAAAAACAGGAAAAATGTATCA	518
	TACTGAA <u>ATAAAATTCTG</u>	519
	CAGAATT <u>TTTCAAGTA</u>	520
Retinoblastoma Gln207Term CAA-TAA	AAAGATCTGAATCTA <u>ACTTTCTTAAAATGTACATT</u> TTT TTCAGGGGAAGTATT <u>ACAATGGAAGATGATCTGGTGATTTC</u> ATT <u>TCAGTTAATGCTATGTGTCCTGACTATT</u> TA	521
	AAAATAGTCAAGGACACATAGCATTAACTGAA <u>ATGAAATCAC</u> CAGATCAT <u>CTTCCATTGTAATACTTCCCCTGAAAAAAAATG</u> TACATTAAAGAA <u>AGTTAGAGATT</u> CAGATCTT	522
	AAGTATT <u>ACAATGGAA</u>	523
	TTCCATT <u>GTAATACTT</u>	524
10 Retinoblastoma Arg251Term CGA to TGA	GTTCTTATCTAATTACCACTTTACAGAAACAGCTGTTACC CATTAATGGTTCACCT <u>CGAACACCCAGGCGAGGTCAGAAC</u> GGAGTGCACGGATAGCAA <u>AAACTAGAAAATGATA</u>	525
	TATCATTTCTAGTTGTTTGCTATCCG <u>IGCACTCCTGTTCTG</u> ACCTCGCCTGGGT <u>TTCGAGGTGAACC</u> ATTAATGGGTATAAC AGCTGTTCTGAA <u>AGTGGTAAATTAGATAAGAAC</u>	526

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GTTCACCT <u>C</u> GAACACCC	527
	GGGTGTT <u>C</u> GAGGTGAAC	528
Retinoblastoma Arg255Term CGA to TGA	TTTACCAC TTT ACAGAAACAGCTGTTAACCCATTAATGGTT CACCTCGAACACCCAGG <u>C</u> GAGGTAGAACACAGGAGTCACG GATAGCAAAACA A CTAGAAAATGATAACAAGAATTATTG	529
	CAATAATTCTGTATCATTCTAGTTGTTTGCTATCCGTGCA CTCCTGTTCTGACCT <u>C</u> GCCTGGGTGTTCGAGGTGAACCATTA ATGGGTATAACAGCTGTTCTGAAAAGTGGTAAA	530
	CACCCAGG <u>C</u> GAGGTAG	531
	CTGACCT <u>C</u> GCCTGGGTG	532
Retinoblastoma Gln266Term CAA to TAA	ATTAATGGTTACCTCGAACACCCAGGCGAGGTAGAACAG GAGTCACGGATAGCAAAACA A CTAGAAAATGATAACAAGAAT TATTGAAGTTCTGTAAAGAACATGAATGTAATATAG	533
	CTATATTACATT C ATGTTCTTACAGAGAA T TCATAATTCTT GTATCATTCTAGTT <u>G</u> TTTGCTATCCGTGCACTCCTGTTCT GACCTCGCCTGGGTGTTCGAGGTGAACCATTAAT	534
	TAGCAAAACA A CTAGAA	535
	TTCTAGTT <u>G</u> TTTGCTA	536
Retinoblastoma Arg320Term CGA to TGA	TGACATGTAAAGGATAATTGTCAGTGACTTTTCTTCAAGG TTGAAAATCTTCTAA <u>A</u> CGATACGAAGAAATTATCTTAAAAAT AAAGATCTAGATGCAAGATTATTTGGATCATG	537
	CATGATCCAAAATAATCTGCATCTAGATCTTATTTAAGA TAAATTCTCGTAT <u>C</u> GTTAGAAAGATTTCACCTTGAAAGA AAAAAGTCACTGACAATTATCCTTACATGTCA	538
	TTCTAA <u>A</u> CGATACGAA	539
	TTCGTAT <u>C</u> GTTAGAAA	540
10 Retinoblastoma Gln354Term CAG to TAG	ACAAATTGTAATTTCAGTATGTGAATGACTTCAC T TATTGTT ATTTAGTTTGAAACACAGAGAACACCACGAAAAAGTAACCTT GATGAAGAGGTGAATGTAATTCCCTCACACACTC	541
	GAGTGTGGAGGAATTACATTACCTCTTCAAGGTTAC TTTTCTGTTGTTCTCT <u>G</u> TGTTCAAAACTAAATAACAATAA GTGAAGTCATTACACACTGAAAATTACAATTGT	542
	TTGAAACACAGAGAACAA	543
	TGTTCTCT <u>G</u> TGTTCAA	544

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Arg358Gly CGA to GGA	TTTCAGTATGTGAATGACTTCACTTATTGTTATTAGTTTGAAACACAGAGAACACC <u>ACG</u> AAAAAGTAACCTTGATGAAGAGGTGAATGTAATTCCCTCACACACTCCAGTTAGGTATG	545
	CATACCTAACTGGAGTGTGTGGAGGAATTACATTACCTCTTCACTCAAGGTTACTTTT <u>C</u> GTGGTGTCTCTGTGTTCAAAACTAAATAACAATAAGTGAAGTCATTACACATACTGAAAA	546
	GAACACCAC <u>CG</u> AAAAAGT	547
	ACTTTT <u>C</u> GTGGTGTTC	548
Retinoblastoma Arg358Term CGA to TGA	TTTCAGTATGTGAATGACTTCACTTATTGTTATTAGTTTGAAACACAGAGAACACC <u>ACG</u> AAAAAGTAACCTTGATGAAGAGGTGAATGTAATTCCCTCACACACTCCAGTTAGGTATG	549
	CATACCTAACTGGAGTGTGTGGAGGAATTACATTACCTCTTCACTCAAGGTTACTTTT <u>C</u> GTGGTGTCTCTGTGTTCAAAACTAAATAACAATAAGTGAAGTCATTACACATACTGAAAA	550
	GAACACCAC <u>CG</u> AAAAAGT	551
	ACTTTT <u>C</u> GTGGTGTTC	552
Retinoblastoma Ser397Term TCA to TAA	CTGTTATGAACACTATCCAACAATTAAATGATGATTAAATTCA <u>G</u> CAAGTGATCAACCTT <u>C</u> AGAAAATCTGATTTCTATTAAACGTAAGCCATATGAAACATTATTATTGTAATAT	553
	ATATTACAATAAAATAATGTTCATATATGGCTACGTTAAAATA <u>G</u> GAAATCAGATTCT <u>G</u> AAGGTTGATCACTGCTGAATTAAAATCATCATTAAATTGTTGGATAGTGTTCATAACAG	554
	TCAACCTT <u>C</u> AGAAAATC	555
	GATT <u>T</u> CT <u>G</u> AAGGTTGA	556
10 Retinoblastoma Arg445Term CGA to TGA	TTTCATAATTGTGATTTCATAAAATAGCAGGCTTATTTC <u>T</u> TTTGTTTGTGTTGAT <u>C</u> GATACAAACTGGAGTCGCTTGATATTACCGAGTAATGGAATCCATGCTAAATCAGTAA	557
	TTACTGATTAAAGCATGGATTCCATTACTCGTAATACAAGCGAACTCCAAGTTGTAT <u>C</u> GCTACAAACAAACAAAAGAAAATA <u>A</u> AGAGCCTGCTATTAGAAAATCACAATTATGAAA	558
	GT <u>TT</u> GTAG <u>C</u> GATACAAA	559
	TTTGTAT <u>C</u> GCTACAAAC	560
15 Retinoblastoma Arg455Term CGA to TGA	GCTCTTATTTC <u>T</u> TTGTTGTTGAT <u>C</u> GCATACAAACTGGAGTCGCTTAAATCA <u>G</u> TAAAGTTAAAACAAATATAAAAAAATT <u>C</u> AGCCG	561

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGGCTGAAATTATGTTTAACCTACTGATTAAGC ATGGATTCCATTACTCGGTAAATACAAGCGAACTCCAAGTTGT ATCGCTACAAACAAACAAAAGAAAATAAGAGC	562
	TGTATTAC <u>CG</u> GAGTAATG	563
	CATTACT <u>CG</u> GTAAATACA	564
Retinoblastoma Arg552Term CGA to TGA	ATCGAAAGTTTATCAAAGCAGAAGGCAACTTGACAAGAGAA ATGATAAAACATTAGAAC <u>CG</u> GATGTGAACATCGAATCATGGAAT CCCTTGATGGCTCTCAGTAAGTAGCTAAATAATTG	565
	CAATTATTTAGCTACTTACTGAGAGGCCATGCAAGGGATTCCAT GATTGATGTTCACATCG <u>TT</u> CTAAATGTTTATCATTCTCTG TCAAGTTGCCCTCTGCTTGATAAAACTTCGAT	566
	ATTTAGAAC <u>CG</u> GATGTGAA	567
	TTCACAT <u>CG</u> TTCTAAAT	568
Retinoblastoma Cys553Term TGT to TGA	AAGTTTATCAAAGCAGAAGGCAACTTGACAAGAGAAATGATA AAACATTAGAAC <u>CG</u> GAT <u>GT</u> GAACATCGAATCATGGAATCCCTG CATGGCTCTCAGTAAGTAGCTAAATAATTGAAGAA	569
	TTCTTCAATTATTTAGCTACTTACTGAGAGGCCATGCAAGGGAT TCCATGATTGATGTT <u>CA</u> CATCGTTCTAAATGTTTATCATTTC TCTTGTCAAGTTGCCCTCTGCTTGATAAAACTT	570
	GAAC <u>CG</u> GAT <u>GT</u> GAACATCG	571
	CGATGTT <u>CA</u> CATCGTT	572
Retinoblastoma Glu554Term GAA to TAA	AGTTTATCAAAGCAGAAGGCAACTTGACAAGAGAAATGATAA AACATTAGAAC <u>CG</u> GAT <u>GT</u> GAACATCGAATCATGGAATCCCTG CATGGCTCTCAGTAAGTAGCTAAATAATTGAAGAAA	573
	TTTCTTCAATTATTTAGCTACTTACTGAGAGGCCATGCAAGGGAA TTCCATGATTGATGTT <u>CA</u> CATCGTTCTAAATGTTTATCATTTC CTCTTGTCAAGTTGCCCTCTGCTTGATAAAACTT	574
	AAC <u>CG</u> GAT <u>GT</u> GAACATCGA	575
	TCGATGTT <u>CA</u> CATCGTT	576
10 Retinoblastoma Ser567Leu TCA to TTA	TACCTGGAAAATTATGCTACTAATGTGGTTTAATTTCATC ATGTTCATAGGATT <u>CA</u> CCTTATTGATCTTAAACAAAT CAAAGGACCGAGAAGGACCAACTGATCACCTGAA	577
	TCAAGGTGATCAGTTGGCCTCTCGGTCTTGATTGTTAA TAAGATCAAATAAGGT <u>GA</u> ATCCTATGAAACATGATGAAAT TAAACCACATTAGTAAGCATAATTCCCAGGTA	578

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATAGGATT <u>CAC</u> CTTAT	579
	ATAAAGGTGAATCCTAT	580
Retinoblastoma Gln575Term CAA to TAA	AATGTGGTTTAATTCATCATGTTCATATAGGATT <u>CAC</u> CTT ATTGATCTTATT <u>AAAC</u> ATCAAAGGACCGAGAAGGACCAACT GATCACCTGAATCTGCTTCCTTAATCTTC	581
	GAAGATTAAGAGGACAAGCAGATTCAAGGTGATCAGTTGGTC CTTCTCGGCCTTGTATT <u>GTT</u> ATAAGATCAAATAAGGTGA ATCCTATATGAAACATGATGAAATTAAAACCACATT	582
	TTATT <u>AAAC</u> ATCAAAG	583
	CTTGATT <u>GTT</u> ATAAA	584
Retinoblastoma Arg579Term CGA to TGA	ATTCATCATGTTCATATAGGATT <u>CAC</u> CTTATTGATCTTAT TAAACAATCAAAGGAC <u>CG</u> GAGAAGGACCAACTGATCACCTGA ATCTGCTTCCTCTTAATCTCCTCCAGAATA	585
	TATTCTGGAGAGGAAGATTAAGAGGACAAGCAGATTCAAGGT GATCAGTTGGCCTCTCG <u>GT</u> CTTGTATTGTTATAAGATC AAATAAAGGTGAATCCTATATGAAACATGATGAAAT	586
	CAAAGGAC <u>CG</u> GAGAAGGA	587
	TCCTTCT <u>CG</u> GTCTTG	588
Retinoblastoma Glu580Term GAA to TAA	TCATCATGTTCATATAGGATT <u>CAC</u> CTTATTGATCTTATTAA ACAATCAAAGGAC <u>CG</u> GAGAAGGACCAACTGATCACCTGAATC TGCTTGTCTCTTAATCTCCTCCAGAATAATC	589
	GATTATTCTGGAGAGGAAGATTAAGAGGACAAGCAGATTCAA GGTGATCAGTTGGCCT <u>CT</u> CGGTCTTGTATTGTTATAAG ATCAAATAAAGGTGAATCCTATATGAAACATGATGA	590
	AGGAC <u>CG</u> GAGAAGGACCA	591
	TGGTC <u>CT</u> CGGTCTT	592
10 Retinoblastoma Ser634Term TCA to TGA	AGAAAAAAAGGTTCAACTACGCGTGTAAATTCTACTGCAAATG CAGAGACACAAGCAAC <u>CT</u> <u>CAG</u> CTTCAGACCCAGAACCCA TTGAAATCTACCTCTTTCACTGTTTATAAAAAAAGG	593
	CCTTTTTATAAAACAGTGAAGAGAGGGTAGATTCAATGGCT TCTGGGTCTGGAAAGGCT <u>GAGG</u> TTGCTGTCTGCATTG CAGTAGAAATTACACCGCGTAGTTGAACCTTTTCT	594
	AGCAAC <u>CT</u> <u>CAG</u> CCTTCC	595
	GGAAGG <u>CT</u> <u>GAGG</u> TTGCT	596

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:	
Retinoblastoma Ala635Pro GCC to CCC	AAAAAAGGTTCAACTACGCGTGTAAATTCTACTGCAAATGCA GAGACACAAGCAACCTCAGCCTCCAGACCCAGAACGCATT GAAATCTACCTCTTTCACTGTTTATAAAAAGGTT	597	
	AACCTTTTATAAAACAGTGAAAGAGAGGTAGATTCAATGG CTTCTGGGTCTGGAAGGCTGAGGTTGCTGTCTGCATT TGCAGTAGAATTACACGCGTAGTTGAACCTTTTT	598	
	CAACCTCAGCCTCCAG	599	
	CTGGAAGGCTGAGGTTG	600	
Retinoblastoma Gln639Ter CAG to TAG	ACTACGCGTGTAAATTCTACTGCAAATGCAGAGACACAAGCA ACCTCAGCCTCCAGACCCAGAACGCATTGAAATCTACCTCT CTTCACTGTTTATAAAAAGGTTAGTAGATGATTA	601	
	TAATCATCTACTAACCTTTTATAAAACAGTGAAAGAGAGGT AGATTCAATGGCTCT <u>GGG</u> TCTGGAAGGCTGAGGTTGCTTG TGTCTCTGCATTGCAGTAGAATTACACGCGTAGT	602	
	TCCAGACCCAGAACCCA	603	
	TGGCTTCT <u>GGG</u> TCTGGA	604	
Retinoblastoma Leu657Pro CTA to CCA	TTGTAATTCAAAATGAACAGTAAAATGACTAATTCTTATT CCCACAGTGTATCGG <u>T</u> AGCCTATCTCCGGCTAAATACACTT TGTGAACGCCTCTGTCTGAGCACCCAGAACATTAGA	605	
	TCTAATTCTGGGTGCTCAGACAGAACGGCGTTACAAAGTGTA TTTAGCCGGAGATAGGCT <u>A</u> GCCGATACACTGTGGGAATAAG AAAAATTAGTCATTTACTGTTCATTTGAATTACAA	606	
	GTATCGG <u>T</u> AGCCTATC	607	
	GATAGGCT <u>A</u> GCCGATAC	608	
Retinoblastoma Arg661Trp CGG to TGG	AATGAACAGTAAAATGACTAATTCTTATTCCCACAGTGTA TCGGCTAGCCTATCT <u>CCGG</u> CTAAATACACTTTGTGAACGCCT TCTGTCTGAGCACCCAGAACATTAGAACATATCATCT	609	
	AGATGATATGTTCTAATTCTGGGTGCTCAGACAGAACGGCGTT CACAAAGTGTATTAGCC <u>GG</u> GAGATAGGCTAGCCGATACACTG TGGGAATAAGAAAAATTAGTCATTTACTGTTCATT	610	
	CCTATCT <u>CCGG</u> CTAAAT	611	
	ATTTAGCC <u>GG</u> GAGATAGG	612	
15	Retinoblastoma Leu662Pro CTA to CCA	AACAGTAAAATGACTAATTCTTATC <u>CC</u> CACAGTGTATCG GCTAGCCTATCTCCGGCTAAATACACTTTGTGAACGCCTCT GTCTGAGCACCCAGAACATTAGAACATATCATCTGGAC	613

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GTCCAGATGATATGTTCTAATTCTGGGTGCTCAGACAGAAGG CGTTCACAAAGTGTATT <u>A</u> GCCGGAGATAGGCTAGCCGATAC ACTGTGGGAATAAGAAAAATTAGTCATTTACTGTT	614
	TCTCCGGCTAAATACAC	615
	GTGTATT <u>A</u> GCCGGAGA	616
Retinoblastoma Glu675Term GAA to TAA	TATCGGCTAGCCTATCTCCGGCTAAATACACTTTGTGAACGC CTTCTGTCTGAGCACCC <u>A</u> GAATTAGAACATATCATCTGGACC CTTTCCAGCACACCCCTGCAGAATGAGTATGAACTCA	617
	TGAGTTCATACTCATTCTGCAGGGTGTGCTGGAAAAGGGTCC AGATGATATGTTCTAATT <u>C</u> TGGGTGCTCAGACAGAAGGCCTT CACAAAGTGTATTAGCCGGAGATAGGCTAGCCGATA	618
	AGCACCC <u>A</u> GAATTAGAA	619
	TTCTAATT <u>C</u> TGGGTGCT	620
Retinoblastoma Gln685Pro CAG to CCG	TTTGTGAACGCCCTCTGCTGAGCACCCAGAATTAGAACATA TCATCTGGACCCCTTCC <u>A</u> GCACACCCCTGCAGAATGAGTATG AACTCATGAGAGACAGGCATTGGACCAAGTAAGAAA	621
	TTTCTTACTTGGTCCAATGCCTGTCTCATGAGTTCTACT CATTCTGCAGGGTGTGCTGGAAAAGGGTCCAGATGATATGTT CTAATTCTGGGTGCTCAGACAGAAGGCCTCACAAA	622
	CCTTTCC <u>A</u> GCACACCC	623
	GGGTGTGCTGGAAAAGG	624
Retinoblastoma Cys706Tyr TGT to TAT	AAAACCATGTAATAAAATTCTGACTACTTTACATCAATTATT TACTAGATTATGATGT <u>G</u> TTCCATGTATGGCATATGCAAAGTGA AGAATATAGACCTAAATTCAAATCATTGTAAC	625
	GTTACAATGATTTGAATTAAAGGTCTATATTCTTCACTTGCA TATGCCATACATGG <u>A</u> ACACATCATAATCTAGTAAATAAATTGA TGTAAAAGTAGTCAGAATTATTACATGGTTT	626
	TATGATGT <u>G</u> TTCCATGT	627
	ACATGG <u>A</u> ACACATCATA	628
10 Retinoblastoma Cys712Arg TGC to CGC	TTCTGACTACTTTACATCAATTATTACTAGATTATGATGTG TTCCATGTATGGCATAT <u>G</u> CAAAGTGAAGAACATAGACCTAAA TTCAAAATCATTGTAACAGCATAACAAGGATCTTC	629
	GAAGATCCTGTATGCTGTTACAATGATTTGAATTAAAGGTC TATATTCTTCACTTG <u>C</u> ATATGCCATACATGGAACACATCATA ATCTAGTAAATAAATTGATGTAAAAGTAGTCAGAA	630

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGGCAT <u>A</u> TGCAAAGTG	631
	CACTTGC <u>A</u> TATGCCAT	632
Retinoblastoma Tyr728Term TAC to TAA	GTATGGCATATGCAAAGTGAAGAATATAGACCTAAATTCAA ATCATTGTAACAGCATA <u>C</u> AAGGATCTCCTCATGCTGTTAG GAGGTAGGTAATTTCATAGTAAGTTTTGATA	633
	TATCAAAAAAA <u>C</u> TTACTATGGAAAATTACCTACCCCTGAACA GCATGAGGAAGATCCT <u>G</u> TATGCTGTTACAATGATTGAATT TAAGGTCTATATTCTTCACTTGCATATGCCATAC	634
	ACAGCATA <u>C</u> AAGGATCT	635
	AGATCCTT <u>G</u> TATGCTGT	636
Retinoblastoma Glu748Term GAG to TAG	TTTTTTTTTTTTTACTGTTCTCCTCAGACATTCAAACGTGT TTTGATCAAAGAAGAG <u>G</u> AGGTATGATTCTATTATAGTATTCTATA ACTCGGTCTTCATGCAGAGACTGAAAACAAATA	637
	TATTTGTTTCAGTCTCTGCATGAAGACCGAGTTAGAATAC TATAATAGAACATCAACT <u>C</u> CTCTTCTTGTCAAAACACGTTGA ATGTCTGAGGAAGAACAGTAAAAAAAAAAAAAA	638
	AAGAAGAG <u>G</u> AGTATGAT	639
	ATCATACT <u>C</u> CTCTTCTT	640
Retinoblastoma Gln762Term CAG to TAG	TTTTGATCAAAGAAGAGGAGTATGATTCTATTATAGTATTCT ATAACTCGGTCTTCATGC <u>A</u> GAGACTGAAAACAAATTTGCA GTATGCTCCACCAGGGTAGGTCAAAAGTATCCTT	641
	AAGGATACTTTGACCTACCCCTGGTGGAA <u>G</u> CATACTGCAAAA TATTTGTTTCAGTCTCT <u>G</u> CATGAAGACCGAGTTAGAATAC TATAATAGAACATCAACTCCTCTTGTCAAAAC	642
	TCTTCATGC <u>A</u> GAGACTG	643
	CAGTCTCT <u>G</u> CATGAAGA	644
10 Retinoblastoma Arg787Term CGA-TGA	TAATCTACTTTTTGTTTGCTCTAGCCCCCTACCTTGTAC CAATACCTCACATTCC <u>T</u> GAAGCCCTACAAGTTCCATGTT ACCCCTACGGATTCTGGAGGGAACATCTATATT	645
	AAATATAGATGTTCCCTCCAGGAATCCGTAAAGGGTGAAC <u>T</u> GAAACTTGTAAAGGGCTTC <u>G</u> AGGAATGTGAGGTATTGGTGACA AGGTAGGGGGCTAGAGCAAAACAAAAAGTAGATTA	646
	ACATTCC <u>T</u> GAAGCCCT	647
	AGGGCTTC <u>G</u> AGGAATGT	648

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Retinoblastoma Ser816Term TCA to TGA	CCTTACGGATTCCCTGGAGGGAACATCTATTTACCCCTGA AGAGTCATATAAAATT <u>CAGAAGGTCTGCCAACACCAAACAA</u> AAATGACTCCAAGATCAAGGTGTGTGTTCTCTTTA	649
	TAAAGAGAAAACACACACCTTGATCTGGAGTCATTTGTTG GTGTTGGCAGACCTCT <u>GAAATTTATGGACTCTTCAGGG</u> GTGAAATATAGATGTTCCCTCCAGGAATCCGTAAGG	650
	TAAAATT <u>CAGAAGGTC</u>	651
	GACCTTCT <u>GAAATT</u> TA	652

EXAMPLE 8
BRCA1 and BRCA2

Breast cancer is the second major cause of cancer death in American women, with an estimated 44,190 lives lost (290 men and 43,900 women) in the US in 1997. While ovarian cancer accounts for fewer deaths than breast cancer, it still represents 4% of all female cancers. In 1994, two breast cancer susceptibility genes were identified: BRCA1 on chromosome 17 and BRCA2 on chromosome 13. When a woman carries a mutation in either BRCA1 or BRCA2, she is at increased risk of being diagnosed with breast or ovarian cancer at some point in her life.

Ford *et al.*, *Am. J. Hum. Genet.* 62: 676-689 (1998) assessed the contribution of BRCA1 and BRCA2 to inherited breast cancer by linkage and mutation analysis in 237 families, each with at least 4 cases of breast cancer. Families were included without regard to the occurrence of ovarian or other cancers. Overall, disease was linked to BRCA1 in an estimated 52% of families, to BRCA2 in 32% of families, and to neither gene in 16%, suggesting other predisposition genes. The majority (81%) of the breast-ovarian cancer families were due to BRCA1, with most others (14%) due to BRCA2. Conversely, the majority (76%) of families with both male and female breast cancer were due to BRCA2. The largest proportion (67%) of families due to other genes were families with 4 or 5 cases of female breast cancer only.

More than 75% of the reported mutations in the BRCA1 gene result in truncated proteins. Couch *et al.*, *Hum. Mutat.* 8: 8-18, 1996. (1996) reported a total of 254 BRCA1 mutations, 132 (52%) of which were unique. A total of 221 (87%) of all mutations or 107 (81%) of the unique mutations are small deletions, insertions, nonsense point mutations, splice variants, and regulatory mutations that result in

truncation or absence of the BRCA1 protein. A total of 11 disease-associated missense mutations (5 unique) and 21 variants (19 unique) as yet unclassified as missense mutations or polymorphisms had been detected. Thirty-five independent benign polymorphisms had been described. The most common mutations were 185delAG and 5382insC, which accounted for 30 (11.7%) and 26 (10.1%), respectively, of all the mutations.

Most BRCA2 mutations are predicted to result in a truncated protein product. The smallest known cancer-associated deletion removes from the C terminus only 224 of the 3,418 residues constituting BRCA2, suggesting that these terminal amino acids are critical for BRCA2 function. Studies (Spain *et al.*, Proc. Natl. Acad. Sci. 96:13920-13925 (1999)) suggest that such truncations eliminate or interfere with 2 nuclear localization signals that reside within the final 156 residues of BRCA2, suggesting that the vast majority of BRCA2 mutants are nonfunctional because they are not translocated into the nucleus.

The attached table discloses the correcting oligonucleotide base sequences for the BRCA1 and BRCA2 oligonucleotides of the invention.

Table 14
BRCA1 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Met-1-Ile ATG to ATT	CTGCGCTCAGGAGGCCTCACCCCTCTGCTCTGGTAAAGTT CATTGGAACAGAAAGAAAT <u>G</u> GATTATCTGCTCTCGCGTTG AAGAAGTACAAAATGTCAATTATGCTATGCAGAAAATC	653
	GATTTCTGCATAGCATTAATGACATTTGTACTTCTTCAACG CGAAGAGCAGATAAAT <u>C</u> CATTCTTCTGTTCCAATGAACCTT ACCCAGAGCAGAGGGTGAGGCCCTCTGAGCCAG	654
	AAAGAAAT <u>G</u> GATTATC	655
	GATAAA <u>ATCC</u> ATTCTT	656
Breast Cancer Val-11-Ala GTA to GCA	CTGGGTAAAGTTCATTGGAACAGAAAGAAATGGATTATCTG CTCTTCGCGTTGAAGAAGTACAAAATGTCAATTATGCTATGCA GAAAATCTTAGAGTGTCCCCTGTCTGGAGTTGAT	657
	ATCAACTCCAGACAGATGGGACACTCTAAGATTTCTGCATA GCATTAATGACATTGT <u>A</u> CTTCTTCAACGCGAAGAGCAGATA AATCCATTCT. TGTGTTCCAATGAACCTTACCCAG	658
	TGAAGAAGTACAAAATG	659

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CATTTTGT <u>ACTTCTTC</u> A	660
Breast Cancer Ile-21-Val ATC to GTC	ATGGATTATCTGCTCTCGCGTTGAAGAAGTACAAAATGTCA TTAATGCTATGCAGAAA <u>AT</u> CTTAGAGTGTCCCATCTGTCTGG AGTTGATCAAGGAACCTGTCTCCACAAAGTGTGACC	661
	GGTCACACTTGTGGAGACAGGTTCTTGATCAACTCCAGAC AGATGGGACACTCTAACAG <u>AT</u> TTCTGCATAGCATTAAATGACATT TTGTACTTCTCAACGCGAAGAGCAGATAAATCCAT	662
	TGCAGAAA <u>AT</u> CTTAGAG	663
	CTCTAACAG <u>AT</u> TTCTGCA	664
Breast Cancer Leu-22-Ser TTA to TCA	ATTATCTGCTCTCGCGTTGAAGAAGTACAAAATGTCACTAA TGCTATGCAGAAA <u>AT</u> CT <u>TA</u> AGAGTGTCCCATCTGTCTGGAGTT GATCAAGGAACCTGTCTCCACAAAGTGTGACCACAT	665
	ATGTGGTCACACTTGTGGAGACAGGTTCTTGATCAACTCC AGACAGATGGGACACT <u>CT</u> <u>AAGA</u> TTCTGCATAGCATTAAATG ACATTTGTACTTCTCAACGCGAAGAGCAGATAAAT	666
	GAAA <u>AT</u> CT <u>TA</u> AGAGTGT <u>TC</u>	667
	GACACT <u>CT</u> <u>AAGA</u> TT <u>TC</u>	668
Breast Cancer Cys-39-Tyr TGT to TAT	AGAAA <u>AT</u> CT <u>TA</u> AGAGTGTCCCATCTGTCTGGAGTTGATCAAGG AACCTGTCTCCACAAAGTGTGACCACAT <u>AT</u> TTGCAA <u>AT</u> TTG CATGCTGAA <u>ACT</u> TC <u>CA</u> ACC <u>AGA</u> AGAAAGGGCCTTC	669
	GAAGGCC <u>CT</u> <u>TT</u> CT <u>CT</u> GGTTGAGAAG <u>TT</u> CAGCATGC <u>AA</u> AT TTGCAA <u>AA</u> AT <u>GT</u> GGT <u>CA</u> ACT <u>TT</u> GTGGAGACAGGTTCTG AT <u>CA</u> ACT <u>CC</u> AGACAG <u>AT</u> GGGAC <u>ACT</u> CT <u>AA</u> G <u>AT</u> TT <u>CT</u>	670
	CACAA <u>AGT</u> GTGACC <u>ACA</u>	671
	TGTGGT <u>CA</u> ACT <u>TT</u> GT <u>G</u>	672
	CACAT <u>AT</u> TTGCAA <u>AT</u> TTG <u>C</u> ATG <u>T</u> G <u>A</u> AA <u>CT</u> CT <u>CA</u> ACC <u>AGA</u> AGAA <u>AGG</u> GC <u>CT</u> <u>TC</u> <u>AC</u> <u>AG</u> <u>T</u> GT <u>CC</u> <u>TT</u> <u>AT</u> GT <u>AA</u> <u>GA</u> <u>AT</u> GT <u>AT</u> AA <u>AC</u> CAA <u>AGG</u> AG <u>GC</u> <u>CT</u> <u>AC</u> <u>AA</u> <u>AG</u> <u>A</u> GT <u>AC</u> <u>G</u> <u>A</u> <u>G</u> <u>AT</u> <u>TT</u> <u>AG</u> <u>T</u> C	673
10 Breast Cancer Cys-61-Gly TGT to GGT	GA <u>CT</u> <u>AA</u> <u>AT</u> CT <u>CG</u> <u>T</u> ACT <u>TT</u> CT <u>GT</u> AG <u>GG</u> CT <u>CC</u> <u>TT</u> <u>GG</u> <u>TT</u> <u>AT</u> <u>AT</u> <u>TC</u> AT <u>TC</u> <u>TT</u> <u>AC</u> <u>AT</u> <u>AA</u> <u>AG</u> <u>GA</u> <u>CA</u> <u>CT</u> <u>GT</u> <u>GA</u> <u>AG</u> <u>GG</u> <u>CC</u> <u>TT</u> <u>CT</u> <u>GT</u> <u>GG</u> <u>TT</u> GAGAAG <u>TT</u> <u>TC</u> <u>AG</u> <u>GT</u> <u>CA</u> <u>AA</u> <u>AT</u> <u>TT</u> <u>GC</u> <u>AA</u> <u>AT</u> <u>AT</u> <u>GT</u> <u>G</u>	674
	CTTC <u>AC</u> <u>AG</u> <u>T</u> GT <u>CC</u> <u>TT</u> <u>TA</u>	675
	TAA <u>AGG</u> <u>AC</u> <u>AT</u> <u>GT</u> <u>GA</u> <u>AG</u>	676

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Leu-63-Stop TTA to TAA	TTTGC AAATTTG CATGCTGAAACTTCTCAACCAGAAGAAAGG GCCTCACAGTGT CC TT TATGAAGAATGATATAACCAAAAGG AGCCTACAAGAAAGTACGAGATTAGTCAC TT GT	677
	ACAAGTTGACTAAATCTGTACTTTCTTAGGCTC TT GG TTATATCATTCTTACAT A AGGACACTGTGAAGGCC TT CTT CTGGTTGAGAAGTT C AGCATGCAA AA ATTGCAA	678
	GTGT CC TT TATGAAGA	679
	TCTTACAT A AGGACAC	680
Breast Cancer Cys-64-Arg TGT to CGT	TGCAAATTTGCATGCTGAAACTTCTCAACCAGAAGAAAGG CCTTCACAGTGT CC TT TAT G AAGAATGATATAACCAAAAGG GCCTACAAGAAAGTACGAGATTAGTCAC TT GT TG	681
	CAACAAGTTGACTAAATCTGTACTTTCTTAGGCTC TT TT GGTTATATCATTCTTAC A AAAGGACACTGTGAAGGCC TT TC TTCTGGTTGAGAAGTT C AGCATGCAA AA ATTGCA	682
	GTC CC TT TAT G AAGAAT	683
	ATTCTTAC A AAAGGAC	684
Breast Cancer Cys-64-Tyr TGT to TAT	GCAAATTTGCATGCTGAAACTTCTCAACCAGAAGAAAGGGC CTTCACAGTGT CC TT TAT G AAGAATGATATAACCAAAAGGAG CCTACAAGAAAGTACGAGATTAGTCAC TT GT GA	685
	TCAACAAGTTGACTAAATCTGTACTTTCTTAGGCTC TT TT TGGTTATATCATTCTTAC A AAAGGACACTGTGAAGGCC TT TC CTTCTGGTTGAGAAGTT C AGCATGCAA AA ATTG C	686
	TCCT TT TAT G AAGAATG	687
	CATTCTTAC A AAAGGA	688
Breast Cancer Gln-74-Stop CAA to TAA	CAGAAGAAAGGGC TT CACAGTGT CC TT TATGAAGAATGAT ATAACCAAAAGGAGC CT ACAAGAAAGTACGAGATTAGTC AA CTTGT GA AGAGCTATTGAAAATCATTGT G CT TT TC	689
	GAAAAGCACAAATGAT TT CAATAGCT TT CAACAGTTGACT AAATCTGTACT TT CTT G AGGCTC TT GGTTATATCATTCT TACATAAAGGACACTGTGAAGGCC TT CTT CT GT	690
	GGAGC CT ACAAGAAAGT	691
	ACT TT CTT G AGGCTCC	692

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Tyr-105-Cys TAT to TGT	AGCTATTGAAAATCATTTGTCTTCAGCTTGACACAGGTTT GGAGTATGCAAACAGCT <u>A</u> TAATTTGCAAAAAGGAAAATAAC TCTCCTGAACATCTAAAGATGAAGTTCTATCAT	693
	ATGATAGAAACTCATCTTAGATGTTAGGAGAGTTATTT CCTTTTTGCAAAATT <u>A</u> AGCTGTTGCATACTCCAAACCTGT GTCAAGCTGAAAAGCACAAATGATTTCAATAGCT	694
	AAACAGCT <u>A</u> TAATTTG	695
	CAAAATT <u>A</u> AGCTGTT	696
Breast Cancer Asn-158-Tyr AAC to TAC	CTACAGAGTGAACCCGAAAATCCTCCTGCAGGAAACCAGT CTCAGTGCCAACTCT <u>A</u> ACCTGGAACTGTGAGAAGCTCTG AGGACAAAGCAGCGGATACAACCTCAAAAGACGTCTG	697
	CAGACGTCTTTGAGGTTGTATCCGCTGCTTCAGAG TTCTCACAGTTCCAAGGT <u>A</u> GAGAGTTGGACACTGAGACTGG TTTCCTGCAAGGAAGGATTTCGGGTTCACTCTGTAG	698
	AACTCT <u>A</u> ACCTGG	699
	TCCAAGGT <u>A</u> GAGAGTT	700
Breast Cancer Gln-169-Stop CAG to TAG	GAAACCAGTCTCAGTGTCCAACTCT <u>A</u> CCCTGGAACTGTG AGAACTCTGAGGACAAAG <u>C</u> AGCGGATACAACCTCAAAAGAC GTCTGTCTACATTGAATTGGGATCTGATTCTCTGAAG	701
	CTTCAGAAGAACATCAGATCCCATT <u>A</u> ATGTAGACAGACGTCTT TTGAGGTTGTATCCGCT <u>G</u> CTTGCCTCAGAGTTCTCACAGT TCCAAGGT <u>A</u> GAGAGTTGGACACTGAGACTGGTTTC	702
	GGACAAAG <u>C</u> AGCGGATA	703
	TATCCGCT <u>G</u> CTTGTCC	704
Breast Cancer Trp-353-Stop TGG to TAG	CTCCCAGCACAGAAAAAAAGGTAGATCTGAATGCTGATCCCC TGTGTGAGAGAAA <u>A</u> AT <u>G</u> GAATAAGCAGAAACTGCCATGCT CAGAGAACCTAGAGATACTGAAGATGTTCTGGAT	705
	ATCCAAGGAACATCTCAGTATCTTAGGATTCTCTGAGCAT GGCAGTTCTGCTTATT <u>C</u> ATTCTTTCTCACACAGGGGAT CAGCATT <u>C</u> AGATCTACCTTTCTGTGCTGGGAG	706
	AAAAGAAT <u>G</u> GAATAAGC	707
	GCTTATT <u>C</u> ATTCTTT	708
Breast Cancer Ile-379-Met ATT to ATG	ATGCTCAGAGAAC <u>C</u> CTAGAGATACTGAAGATGTTCTGGAT AACACTAA <u>A</u> AGCAGCAT <u>I</u> CAGAAAGTTAATGAGTGTTCC AGAAGTGATGA <u>A</u> CTGTTAGGTTCTGATGACTCACAT	709

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGTGAGTCATCAGAACCTAACAGTTCATCACTCTGGAAAAC CACTCATTAACTTCTGA <u>A</u> ATGCTGCTATTAGTGTATCCAAG GAACATCTCAGTATCTCTAGGATTCTGAGCAT	710
	AGCAGCATT <u>C</u> AGAAAGT	711
	ACTTTCTGA <u>A</u> ATGCTGCT	712
Breast Cancer Glu-421-Gly GAA to GGA	GGGAGTCTGAATCAAATGCCAAAGTAGCTGATGTATTGGACG TTCTAAATGAGGTAGAT <u>G</u> AAATATTCTGGTCTTCAGAGAAAAT AGACTTACTGCCAGTGATCCTCATGAGGCTTAAT	713
	ATAAAGCCTCATGAGGATCACTGCCAGTAAGTCTATTCT CTGAAGAACAGAA <u>T</u> ATCATCTACCTCATTTAGAACGTCCAA TACATCAGCTACTTGGCATTGATTGAGACTCCC	714
	GGTAGAT <u>G</u> AAATATTCTG	715
	CAGAATATT <u>C</u> ATCTACC	716
	ATATGAAAAGTGAAGAGAGTTCACTCCAAATCAGTAGAGAGTA ATATTGAAGACAA <u>A</u> AT <u>T</u> GGGAAAACCTATCGGAAGAAGG CAAGCCTCCCCAACTTAAGCCATGTA <u>A</u> CTGAAATC	717
Breast Cancer Phe-461-Leu TTT to CTT	GATTTCA <u>G</u> TTACATGGCTTAAGTTGGGGAGGC <u>T</u> GCCTCT TCCGATAGGTTTCCAA <u>A</u> TTTTGTCTCAATATTACTCTCT ACTGATTGGAGTGA <u>A</u> CTCTTCACTTTACATAT	718
	ACAAA <u>A</u> TTGGGAA	719
	TTTCCCA <u>A</u> TTTTGT	720
	GAAAGAGTTCACTCCAAATCAGTAGAGAGTAATATTGAAGAC AAAATATTGGGAAAAC <u>C</u> TATCGGAAGAAGGCAAGCCTCCCC AACTTAAGCCATGTA <u>A</u> CTGAAAATCTAATTAGGAG	721
Breast Cancer Tyr-465-Leu TAT to GAT	CTCCTATAATTAGATTTCAGTTACATGGCTTAAGTTGGGGAG GCTTGCCTTCTCCGAT <u>A</u> GGTTTCCAA <u>A</u> TTTTGTCTCA ATATTACTCTACTGATTGGAGTGA <u>A</u> CTCTTC	722
	GGAAA <u>A</u> CC <u>T</u> ATCGGAAG	723
	CTTCCGAT <u>A</u> GGTTTCC	724
	ACCTATCGGAAGAAGGCAAGCCTCCCCAACTTAAGCCATGTA ACTGAAAATCTAATT <u>A</u> GGAGCATTGTTACTGAGCCACAGA TAATACAAGAGCGTCCCCTCACAA <u>A</u> TTAAAGC	725
10 Breast Cancer Gly-484-Stop GGA to TGA	GCTTTAATTATTTGTGAGGGGACGCTCTGTATTATCTGTGG CTCAGTAACAA <u>A</u> CTGCT <u>C</u> TATAATTAGATTTCAGTTACATGG CTTAAGTTGGGGAGGCTGCCTTCCGATAGGT	726

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAATTATAG <u>G</u> GACATT	727
	AAATGCTCCTATAATTA	728
Breast Cancer Arg-507-Ile AGA to ATA	TTACTGAGCCACAGATAATACAAGAGCGTCCCCTCACAAATA AATTAAAGCGTAAAGGAG <u>A</u> CCCTACATCAGGCCTTCATCCTG AGGATTTATCAAGAAAGCAGATTGGCAGTTCAAAA	729
	TTTGAACTGCCAAATCTGCTTCTTGATAAAATCCTCAGGAT GAAGGCCTGATGTAGGT <u>C</u> TCCCTTACGCTTAATTTATTGT GAGGGGACGCTTGTATTATCTGTGGCTCAGTAA	730
	TAAAAGGAG <u>A</u> CCCTACAT	731
	ATGTTAGGT <u>C</u> TCCCTTAA	732
	CACAGATAATACAAGAGCGTCCCCTCACAAATAAAATTAAAGC GTAAAAGGAGACCTACAT <u>C</u> AGGCCTTCATCCTGAGGATTAA TCAAGAAAGCAGATTGGCAGTTCAAAGACTCCTGA	733
Breast Cancer Ser-510-Stop TCA to TGA	TCAGGAGTCTTGA <u>A</u> CTGCCAAATCTGCTTCTTGATAAAAT CCTCAGGATGAAGGC <u>C</u> T <u>G</u> ATGTAGGTCTCCCTTACGCTTA ATTTATTTGTGAGGGGACGCTTGTATTATCTGTG	734
	ACCTACAT <u>C</u> AGGCCTTC	735
	GAAGGCCT <u>G</u> ATGTAGGT	736
	AGGAGACCTACATCAGGCCTTCATCCTGAGGATTAAATCAAG AAAGCAGATTGGCAGTT <u>C</u> AAAAGACTCCTGAAATGATAAATC AGGGAACTAACCAACGGAGCAGAATGGTCAAGTGA	737
	TCACTTGACCATTCTGCTCCGTTGGTAGTTCCCTGATTAT CATTTCAGGAGTCTT <u>G</u> AACTGCCAAATCTGCTTCTTGATA AAATCCTCAGGATGAAGGCCTGATGTAGGTCTCCT	738
Breast Cancer Gln-526-Stop CAA to TAA	TGGCAGTT <u>C</u> AAAAGACT	739
	AGTCTT <u>T</u> GA <u>A</u> CTGCCA	740
	AGGAGACCTACATCAGGCCTTCATCCTGAGGATTAAATCAAG AAAGCAGATTGGCAGTT <u>C</u> AAAAGACTCCTGAAATGATAAATC AGGGAACTAACCAACGGAGCAGAATGGTCAAGTGA	741
	TCACTTGACCATTCTGCTCCGTTGGTAGTTCCCTGATTAT CATTTCAGGAGTCTT <u>G</u> AACTGCCAAATCTGCTTCTTGATA AAATCCTCAGGATGAAGGCCTGATGTAGGTCTCCT	742
	AAACGGAG <u>C</u> AGAATGGT	743
10 Breast Cancer Gln-541-Stop CAG to TAG	ACCATTCTGCTCCGTT	744

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Gly-552-Val GGT to GTT	TAAATCAGGGAACTAACCAACGGAGCAGAATGGTCAGTGA TGAATATTACTAATAG <u>GGT</u> CATGAGAATAAACAAGGTGA TTCTATTAGAATGAGAAAATCCTAACCCAATAGA	745
	TCTATTGGGTTAGGATTTCTCATTCTGAATAGAATCACCTT TGTTTTATTCTCATG <u>ACC</u> ACTATTAGTAATATTCACTTGAC CATTCTGCTCCGTTGGTAGTCCCTGATT	746
	TAATAGT <u>GGT</u> CATGAGA	747
	TCTCATG <u>ACC</u> ACTATT	748
Breast Cancer Gln-563-Stop CAG to TAG	GGTCAAGTGTGAATATTACTAACATAGTGGTCATGAGAATAAA CAAAGGTGATTCTATT <u>CAGA</u> ATGAGAAAATCCTAACCCAAT AGAATCACTCGAAAAAGAATCTGCTTCAAAACGA	749
	TCGTTTGAAAGCAGATTCTTTCGAGTGATTCTATTGGGTT AGGATTTCTCAT <u>CTGA</u> ATAGAATCACCTTTGTTTATTCT CATGACCACATTAGTAATATTCACTTGACC	750
	ATTCTATT <u>CAGA</u> ATGAG	751
	CTCATTCTGAATAGAAT	752
Ovarian Cancer Lys-607-Stop AAA to TAA	ATAAGCAGCAGTATAAGCAATATGGAAC T CGAATTAAATATCC ACAATTCAAAGCAC <u>CTAAA</u> AGAATAGGCTGAGGAGGAAGT CTTCTACCAGGCATATT <u>CATGCGCT</u> GA T ACTAGTAG	753
	CTACTAGTTCAAGCGCATGAATATGCC T GGTAGAAGACTTCC TCCTCAGCCTATTCTTT <u>TAGGTGCT</u> TTGAATTGTGGATATT TAATTCGAGTTCCATATTGCTTAA <u>CTGCT</u> TTAT	754
	AAGCAC <u>CTAAA</u> GAAT	755
	ATTCTTT <u>TAGGTGCT</u>	756
10 Breast Cancer Leu-639-Stop TTG to TAG	ATATT <u>CATGCGCT</u> GA A CTAGTAGCAGTAGAAATCTAACCCC ACCTAATTGTA <u>CTGA</u> ATT <u>GCA</u> ATTGATAGTTGTTAGCAGT GAAGAGATAAAGAAAAAAAGTACAACCAATGCC	757
	GGCATTGGTTGTACTTTTCTTAT <u>CTCTT</u> CACTGCTAGA ACA <u>ACTATCA</u> ATT <u>GC</u> AATT <u>CA</u> GTACAATTAGGTGGGCTTAGA TTT <u>CTACTGACT</u> ACTAGTTCAAGCGCATGAATAT	758
	TACT <u>GAAT</u> <u>GCA</u> ATT <u>CA</u> GT	759
	CAATT <u>TCGA</u> ATT <u>CA</u> GT	760
15 Breast Cancer Asp-693-Asn GAC to AAC	GAACCTGCAACTGGAGCCAAGAAGAGTAACAAGCCAAATGAA CAGACAAGTAAAGACAT <u>GACAGCG</u> AT <u>ACT</u> TTCCCAGAGCTG AAGTTAACAAATGCAC <u>CTGG</u> TTCTTACTAAGTGT	761

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:	
	AACACTTAGAAAAGAACCGAGGTGCATTGTTAACTTCAGCTC TGGGAAAGTATCGCTGT <u>CATGTCTTACTGTCTGTTCA</u> TT GGCTTGTTACTCTCTGGCTCCAGTGCAGGGTC	762	
	AAAGACAT <u>GACAGCGAT</u>	763	
	ATCGCTGT <u>CATGTCTT</u>	764	
Ovarian Cancer Glu-720-Stop GAA to TAA	CTGAAGTTAACAAATGCACCTGGTTCTTACTAAGTGTCAA ATACCAGTGA <u>ACTTAAAGAATTGTC</u> ATCCTAGCCTCCAAG AGAAGAAAAAGAAGAGAAA <u>ACTAGAACAGTTAAAG</u>	765	
	CTTTA <u>ACTGTTCTAGTTCTCTTCTTTCTTCTTGGAGG</u> CTAGGATTGACA <u>AAATTCTTTAAGTTCACTGGTATTGAA</u> ACT TAGTAAAGAACCA <u>CCAGGTGCATTGTTAACTTCAG</u>	766	
	AACTTAA <u>AGAATTGTC</u>	767	
	GACAA <u>ATTCTTTAAGTT</u>	768	
Breast Cancer Glu-755-Stop GAA to TAA	CTAGAAACAGTTAAAGTGTCTAAC <u>ATGCTGAAGACCCC</u> AAA GATCTCATGTTAAGTGG <u>GAAAGGGTTTGCAA</u> ACTGAAAGA TCTGTAGAGAGTAGCAGTATT <u>CATTGGTACCTGGTA</u> CTGGTA	769	
	TACCAGGTACCA <u>ATGAAACTGCTACTCTCACAGATCTTC</u> AGTTGCAA <u>AAACCC</u> TT <u>CTCCACTTAACATGAGATCTTGGGG</u> TCTTCAGCATTATTAGAC <u>ACTTTAACTGTTCTAG</u>	770	
	TAAGTGG <u>GAGAAAGGGTT</u>	771	
	AACC <u>CTTCTCCACTTA</u>	772	
Breast Cancer Ser-770-Stop TCA to TAA	TCATGTTAAGTGGAGA <u>AGGGTTTGCAA</u> ACTGAAAGATCTG TAGAGAGTAGCAGTATT <u>CATTGGTACCTGGTACTGATTATG</u> GCACTCAGGAA <u>AGTATCTCGTTACTGGAAGTTAGCAC</u>	773	
	GTGCTAA <u>CTCCAGTAACGAGATACTT</u> CCTGAGTGCCATAA TCAGTACCA <u>GGTACCAATGAA</u> ACTGCTACTCTCACAGAT CTT <u>TCAGTTGCAA</u> AAACCC <u>TTCTCCACTTAACATGA</u>	774	
	CAGTATT <u>CATTGGTAC</u>	775	
	GTACCA <u>ATGAAACTG</u>	776	
10	Breast Cancer Val-772-Ala GTA to GCA	TAAGTGGAGA <u>AGGGTTTGCAA</u> ACTGAAAGATCTGTAGAGA GTAGCAGTATT <u>CATTGGTACCTGGTACTGATTATGGCACTC</u> AGGAA <u>AGTATCTCGTTACTGGAAGTTAGCACTCTAGG</u>	777
	CCTAGAGTGCTAA <u>CTCCAGTAACGAGATACTT</u> CCTGAGTGC CCATAAT <u>CGTACCAAGGTACCAATGAA</u> ACTGCTACTCTCA CAGAT <u>CTTCAGTTGCAA</u> AAACCC <u>TTCTCCACTTA</u>	778	

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTCATTGGTACCTGGTA	779
	TACCAGGT <u>ACCAATGAA</u>	780
Breast Cancer Gln-780-Stop CAG to TAG	ACTGAAAGATCTGTAGAGAGTAGCAGTATTCAATTGGTACCT GGTACTGATTATGGCACT <u>CAGGAAAGTATCTCGTTACTGGAA</u> GTTAGCACTCTAGGGAAGGAAAAACAGAACCAAATA	781
	TATTTGGTCTGTTTGCCTCCCTAGAGTGCTAACTCCAG TAACGAGATACTTCCT <u>GAGTGCCATAATCAGTACCAAGGTAC</u> CAATGAAAATCTGCTACTCTACAGATCTTCAGT	782
	ATGGCACT <u>CAGGAAAGT</u>	783
	ACTTCCT <u>GAGTGCCAT</u>	784
Breast Cancer Glu-797-Stop GAA to TAA	TATGGCACTCAGGAAAGTATCTCGTTACTGGAAGTTAGCACT CTAGGGAAGGCAAAACAGAACCAAATAAATGTGTGAGTCAG TGTGCAGCATTGAAAACCCAAGGGACTAATTCA	785
	CATGAATTAGTCCCTGGGGTTTCAAATGCTGCACACTGAC TCACACATTATTGGT <u>CTGTTTGCCTCCCTAGAGTGCT</u> AACTCCAGTAACGAGATACTTCCTGAGTGCCATA	786
	CAAAAACAGAACCAAAT	787
	ATTTGGTCTGTTTGT	788
Breast Cancer Lys-820-Glu AAA to GAA	AAATGTGTGAGTCAGTGTGCAGCATTGAAAACCCAAGGGA CTAATTCA <u>GGTTGTTCCA</u> AAAGATAATAGAAATGACACAGAAC GCTTAAGTATCCATTGGACATGAAGTTAACCA	789
	TGTGGTTAACTCATGTCCCATTGGACTTAAAGCCTCTGT GTCATTCTATTATCTT <u>GGACAACCATGAATTAGTCCCTTG</u> GGGTTTCAAATGCTGCACACTGACTCACACATT	790
	GTTGTT <u>CCA</u> AAAGATAAT	791
	ATTATCTTGGAAACAAC	792
Breast Cancer Thr-826-Lys ACA to AAA	CAGCATTGAAAACCCAAGGGACTAATTCA <u>GGTTGTTCCA</u> AAGATAATAGAAATGACACAGAAC <u>GGCTTAAAGTATCCATTGG</u> GACATGAAGTTAACCA <u>AGTCGGAAACAAGCATAGA</u>	793
	TCTATGCTTGGTCCGACTGTGGTTAACTCATGTCCCATTG GATACTAAAGCCTCTGTGCATTCTATTATCTTGGAAACA ACCATGAATTAGTCCCTGGGGTTTCAAATGCTG	794
	AAATGACAC <u>AGAACGGCT</u>	795
	AGCCTTCT <u>GTCATT</u>	796

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Arg-841-Trp CGG to TGG	GATAATAGAAATGACACAGAAGGCTTAAGTATCCATTGGGA CATGAAGTTAACACACAGTC <u>GGGAAACAAGCATAGAAATGGAA</u> GAAAGTGAACCTGATGCTAGTATTGCAGAATACAT	797
	ATGTATTCTGCAAATACTGAGCATCAAGTTCACTTCTTCAT TTCTATGCTTGTCCC <u>GACTGTGGTTAACTTCATGTCCCAAT</u> GGATACTAAAGCCTCTGTGTCAATTCTATTATC	798
	ACCACAGTC <u>GGGAAACA</u>	799
	TGTTTCCC <u>GACTGTGGT</u>	800
Breast Cancer Pro-871-Leu CCG to CTG	AACTTGATGCTCAGTATTGAGAATACATTCAAGGTTCAA GCGCCAGTCATTGCT <u>CCGTTCAAATCCAGGAAATGCAGA</u> AGAGGAATGTGCAACATTCTGCCACTCTGGTC	801
	GACCCAGAGTGGGCAGAGAATGTTGCACATTCCCTCTGCA TTTCCTGGATTGAAAAC <u>GGAGCAAATGACTGGCGCTTGAA</u> ACCTTGAATGTATTCTGCAAATACTGAGCATCAAGTT	802
	ATTTGCT <u>CCGTTCAA</u>	803
	TTGAAAAC <u>GGAGCAAAT</u>	804
Breast Cancer Leu-892-Ser TTA to TCA	TTTCAAATCCAGGAAATGCAGAAGAGGAATGTGCAACATTCT CTGCCCACTCTGGTCCT <u>AAAGAAACAAAGTCCAAAAGTCA</u> CTTTGAATGTGAACAAAGGAAGAAAATCAAGGAAA	805
	TTTCCTTGATTTCTTCCTTGTTCACATTCAAAGTGACTTT TGGACTTTGTTCTT <u>AAGGACCCAGAGTGGGCAGAGAATGT</u> TGCACATTCCCTCTGCATTCTGGATTGAAA	806
	TGGGT <u>CCCTAAAGAAC</u>	807
	TTTCTT <u>AAAGGACCCA</u>	808
10 Breast Cancer Glu-908-Stop GAA to TAA	CACTCTGGGTCTTAAAGAAACAAAGTCCAAAAGTC <u>ACTTTG</u> AATGTGAACAAAGGAAG <u>AAAATCAAGGAAAGAATGAGTCTA</u> ATATCAAGCCTGTACAGACAGTTAATATCACTGCAG	809
	CTGCAGTGATATTAACTGTC <u>GTACAGGCTTGATATTAGACTC</u> ATTCTTC <u>CTTGATTTCTTCC</u> TTTGTTCACATTCAAAGTGA CTTTGGACTTTGTTCTTAAAGGACCCAGAGTG	810
	AAAAGGAAG <u>AAAATCAA</u>	811
	TTGATT <u>TTCTCC</u> TTT	812
15 Breast Cancer Gly-960-Asp GGC to GAC	ATAATGCCAAATGTAGTATCAAAGGAGGCTTAGGTTTGCT ATCATCTCAGTT <u>CAGAGGCAACGAAACTGGACTCATTACTCC</u> AAATAAACATGGACTTTACAAAACCCATATCGTAT	813

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:	
	ATACGATATGGGTTTGTAAAAGTCATGTTATTGGAGTAA TGAGTCCAGTTCGTT <u>G</u> CCTCTGA <u>A</u> CTGAGATGATAGACAAA ACCTAGAGCCTCCTTGATA <u>T</u> ACTACATTGGCATTAT	814	
	GTTCAGAG <u>G</u> CAACGAAA	815	
	TTTCGTT <u>G</u> CCTCTGAAC	816	
Breast Cancer Met-1008-Ile ATG to ATA	ATTTGTTAAA <u>A</u> CTAA <u>T</u> GTAA <u>G</u> AAA <u>A</u> CTGCTAGAGGAAAAC TTTGAGGA <u>A</u> CA <u>T</u> TC <u>A</u> AT <u>G</u> T <u>C</u> AC <u>C</u> TGAA <u>A</u> AGAGAA <u>A</u> GG <u>A</u> AT GAGAAC <u>A</u> TT <u>C</u> CA <u>A</u> GT <u>A</u> CT <u>G</u> G <u>A</u> C <u>A</u> ATT <u>G</u> CC <u>G</u> T	817	
	ACGGCTAATTGTGCTCA <u>T</u> GTACTTG <u>G</u> A <u>T</u> GTTCTCATTTCCC ATTTCTCTTC <u>C</u> AGGT <u>G</u> AC <u>T</u> TA <u>G</u> ATGTT <u>C</u> CTCAA <u>A</u> GT <u>T</u> TCCT CTAGCAGATTTCTTACATT <u>T</u> AGTTTAACAA <u>A</u> AT	818	
	CATT <u>C</u> AA <u>T</u> <u>G</u> T <u>C</u> AC <u>C</u> T <u>G</u> A	819	
	TCAGGT <u>G</u> AC <u>T</u> TA <u>G</u> AT <u>G</u>	820	
Breast Cancer Thr-1025-Ile ACA to ATA	ACTTTGAGGA <u>A</u> CA <u>T</u> TC <u>A</u> AT <u>G</u> T <u>C</u> AC <u>C</u> TGAA <u>A</u> AGAGAA <u>A</u> GG <u>A</u> ATGAGAAC <u>A</u> TT <u>C</u> CA <u>A</u> GT <u>A</u> <u>C</u> AGT <u>G</u> AG <u>C</u> ACA <u>A</u> TT <u>G</u> CC <u>G</u> T <u>A</u> ATA ACATTAGAGAA <u>A</u> ATGTTTTAA <u>A</u> AGA <u>A</u> GG <u>C</u> AG <u>C</u> T <u>A</u> AG	821	
	CTTGAGCTGGCTTCTTAAA <u>A</u> ACATTTC <u>T</u> CT <u>C</u> TA <u>A</u> AT <u>G</u> T <u>T</u> ATT <u>A</u> CG GCT <u>A</u> TT <u>G</u> T <u>G</u> CT <u>C</u> ACT <u>G</u> T <u>A</u> CTTG <u>G</u> A <u>T</u> GTTCTCATTTCCC <u>A</u> TT TCTCTTC <u>C</u> AGGT <u>G</u> AC <u>T</u> TA <u>G</u> ATGTT <u>C</u> CTCAA <u>A</u> GT	822	
	TCCAAG <u>T</u> AC <u>A</u> GT <u>G</u> AG <u>CA</u>	823	
	TGCT <u>C</u> ACT <u>G</u> T <u>A</u> CTTG <u>G</u> A	824	
Breast Cancer Glu-1038-Gly GAA to GGA	ACATT <u>C</u> CA <u>A</u> GT <u>A</u> CT <u>G</u> G <u>A</u> CC <u>A</u> ATT <u>G</u> CC <u>G</u> T <u>A</u> ATA <u>A</u> C <u>A</u> TT <u>A</u> G <u>A</u> AAA <u>A</u> TTGTTTTAA <u>A</u> AG <u>A</u> AG <u>C</u> C <u>A</u> G <u>C</u> T <u>A</u> AG <u>C</u> AA <u>A</u> TT <u>A</u> AT <u>G</u> AA GTAGG <u>T</u> CC <u>A</u> GT <u>A</u> CT <u>A</u> AT <u>G</u> A <u>A</u> GT <u>G</u> G <u>C</u> T <u>C</u> AG <u>T</u> AT	825	
	ATACTGGAGCCC <u>A</u> TT <u>C</u> ATT <u>A</u> GT <u>T</u> ACT <u>G</u> GA <u>A</u> C <u>C</u> T <u>A</u> CT <u>T</u> CT <u>A</u> AA TATTGCTTG <u>G</u> ACT <u>G</u> G <u>C</u> T <u>T</u> CTTAAA <u>A</u> ACATTTC <u>T</u> CT <u>A</u> AT <u>G</u> TT <u>A</u> TTACGG <u>C</u> TA <u>A</u> TT <u>G</u> T <u>G</u> CT <u>C</u> ACT <u>G</u> T <u>A</u> CTTG <u>G</u> A <u>T</u> G	826	
	TTTTAA <u>A</u> AG <u>A</u> GG <u>C</u> C <u>A</u> G <u>C</u> T	827	
	AG <u>C</u> T <u>G</u> G <u>C</u> T <u>T</u> CTTAAA <u>A</u>	828	
10	Breast Cancer Ser-1040-Asn AGC to AAC	CAAGT <u>A</u> CT <u>G</u> G <u>A</u> CC <u>A</u> ATT <u>G</u> CC <u>G</u> T <u>A</u> ATA <u>A</u> C <u>A</u> TT <u>A</u> GT <u>G</u> AG <u>A</u> AA ATGTTTTAA <u>A</u> AG <u>A</u> AG <u>C</u> C <u>A</u> <u>G</u> C <u>T</u> CA <u>A</u> GT <u>C</u> AA <u>A</u> TT <u>A</u> AT <u>G</u> A <u>A</u> GT <u>G</u> AG <u>T</u> AG <u>G</u> TTCC <u>A</u> GT <u>A</u> CT <u>A</u> AT <u>G</u> A <u>A</u> GT <u>G</u> G <u>C</u> T <u>C</u> AG <u>T</u> AT <u>A</u> AT <u>G</u> A	829
	TCATTA <u>A</u> ACT <u>G</u> G <u>A</u> G <u>C</u> CC <u>A</u> CT <u>T</u> CT <u>A</u> TT <u>A</u> GT <u>T</u> ACT <u>G</u> GA <u>A</u> C <u>C</u> T <u>A</u> CT <u>T</u> CTTA <u>A</u> AT <u>T</u> G <u>C</u> TT <u>G</u> AG <u>C</u> T <u>G</u> G <u>C</u> TT <u>A</u> AA <u>A</u> ACATTTC <u>T</u> CT <u>A</u> AT <u>G</u> T <u>T</u> ATGTTATT <u>A</u> CG <u>G</u> CT <u>A</u> AT <u>G</u> T <u>G</u> CT <u>C</u> ACT <u>G</u> T <u>A</u> CTTG	830	

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:	
	AGAAGCC <u>A</u> GCTCAAGCA	831	
	TGCTTGAG <u>C</u> GGCTTCT	832	
Breast Cancer Val-1047-Ala GTA to GCA	GCCGTAAACATTAGAGAAAATGTTTAAAGAACGCCAGCTC AAGCAATATTAAATGAAG <u>T</u> AGGTTCCAGTACTAATGAAGTGGG CTCCAGTATTAAATGAAATAGGTTCCAGTGATGAAAA	833	
	TTTCATCACTGGAACCTATTCAATTAAACTGGAGCCCACTT CATTAGTACTGGAACCT <u>A</u> CTTCATTAAATTGCTTGAGCTGGC TTCTTAAAACATTCTCAATGTTATTACGGC	834	
	TAATGAAG <u>T</u> AGGTTCCA	835	
	TGGAACCT <u>A</u> CTTCATTA	836	
Breast Cancer Leu-1080-Stop TTG to TAG	AAATAGGTTCCAGTGATGAAAACATTCAAGCAGAACTAGGTA GAAACAGAGGGCCAAAT <u>T</u> GAATGCTATGCTTAGATTAGGGG TTTGCAACCTGAGGTCTATAAACAAAGTCTTCCTGG	837	
	CCAGGAAGACTTTGTTATAGACCTCAGGTTGCAAAACCCCT AATCTAACGATAGCATT <u>C</u> ATTGGCCCTCTGTTCTACCTA GTTCTGCTGAATGTTTCATCACTGGAACCTATT	838	
	GCCAAAAT <u>T</u> GAATGCTA	839	
	TAGCATT <u>C</u> AAATTGGC	840	
Breast Cancer Leu-1086-Stop TTA to TGA	AAAACATTCAAGCAGAACTAGGTAGAACAGAGGGCCAAAT TGAATGCTATGCTTAGAT <u>T</u> AGGGGTTTGCAACCTGAGGTCT ATAAACAAAGTCTTCCTGGAAGTAATTGTAAGCATCC	841	
	GGATGCTTACAATTACTCCAGGAAGACTTTGTTATAGACCT CAGGTTGCAAAACCCCT <u>A</u> ATCTAACGATAGCATTCAATTGG GCCCTCTGTTCTACCTAGTTCTGCTGAATGTTT	842	
	GCTTAGATT <u>T</u> AGGGGTTT	843	
	AAACCCCT <u>A</u> ATCTAACG	844	
10	Breast Cancer Ser-1130-Stop TCA to TGA	AGCAAGAATATGAAGAAGTAGTTCAGACTGTTAACAGATT CTCTCCATATCTGATT <u>C</u> AGATAACTTAGAACAGCCTATGGGA AGTAGTCATGCATCTCAGGTTGTTCTGAGACACC	845
	GGTGTCTCAGAACAAACCTGAGATGCATGACTACTTCCCAT GGCTGTTCAAGTTCT <u>G</u> AAATCAGATATGGAGAGAAATCT GTATTAACAGTCTGAACACTTCTTCATATTCTTGCT	846	
	TCTGATT <u>T</u> CAGATAACT	847	
	AGTTATCT <u>G</u> AAATCAGA	848	

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Lys-1183-Arg AAA to AGA	CTAGTTTGCTGAAAATGACATTAAGGAAAGTCTGCTGTTT TAGCAAAAGCGTCCAGA <u>A</u> AGGAGAGCTAGCAGGAGTCCTA GCCCTTCACCCATAACACATTGGCTCAGGGTTACCG	849
	CGGTAACCCTGAGCAAATGTATGGGTGAAAGGGCTAGG ACTCCTGCTAACGCTCTCCT <u>T</u> CTGGACGCTTTGCTAAAAACA GCAGAACCTTCCTTAATGTCA <u>T</u> TCAGCAAAACTAG	850
	CGTCCAGA <u>A</u> AGGAGAGC	851
	GCTCTCCT <u>T</u> CTGGACG	852
Breast Cancer Gln-1200-Stop CAG to TAG	AGCGTCCAGAAAGGAGAGCTAGCAGGAGTCCTAGCCCTT CACCCATACACATTGGCT <u>C</u> AGGGTTACCGAAGAGGGCCA AGAAATTAGAGTCCTCAGAAGAGAACCTATCTAGTGAGG	853
	CCTCACTAGATAAGTTCTCTTGAGGACTCTAAC <u>T</u> TTCTGGC CCCTCTCGGTAA <u>C</u> CTGAGCCAAATGTATGGGTGAAAGG GCTAGGACTCCTGCTAACGCTCTCCTTCTGGACGCT	854
	ATTTGGCT <u>C</u> AGGGTTAC	855
	GTAACCCT <u>G</u> AGCCAAAT	856
Breast Cancer Arg-1203-Stop CGA to TGA	AAAGGAGAGCTAGCAGGAGTCCTAGCCCTTCACCCATA <u>C</u> CATTTGGCT <u>C</u> AGGGTTAC <u>C</u> GAAGAGGGGCCAAAGAAATTAGA GTCCTCAGAAC <u>G</u> AGAAC <u>T</u> ATCTAGTGAGGATGAAGAGC	857
	GCTCTTCATCCTCACTAGATAAGTTCTCTTGAGGACTCTAA TTTCTTGCCCCCTT <u>C</u> GGTAACCC <u>T</u> GAGCCAAATGTATG GGTGAAGGGCTAGGACTCCTGCTAACGCTCTCCTT	858
	AGGGTTAC <u>C</u> GAAGAGGG	859
	CCCTCTCGGTAA <u>C</u> CCCT	860
Breast Cancer Glu-1214-Stop GAG to TAG	ACCCATACACATTGGCTCAGGGTTACCGAAGAGGGCCA <u>A</u> GAAATTAGAGTCCTCAG <u>A</u> AGAGAAC <u>T</u> ATCTAGTGAGGATGA AGAGCTCCCTGCTCCA <u>A</u> ACTTGT <u>T</u> TTGGTAAAG	861
	CTTACCAAAATAACAAGTGTGGAA <u>G</u> AGCAGGGAGCTCTCAT CCTCACTAGATAAGTTCTCTTGAGGACTCTAAC <u>T</u> TTCTGGC CCCTCTCGGTAA <u>C</u> CC <u>T</u> GAGCCAAATGTATGGGT	862
	CCTCAGAAC <u>G</u> AGAAC <u>T</u> TA	863
	TAAGTTCTCTTGAGG	864
Breast Cancer Glu-1219-Asp GAG to GAC	TCAGGGTTACCGAAGAGGGCCA <u>A</u> AGAAATTAGAGTCCTCAG AAGAGAAC <u>T</u> ATCTAGTG <u>G</u> AGGATGAAGAGCTCCCTGCTCC AACACTTGT <u>T</u> TTGGTAAAGTAACAA <u>T</u> ACCTTCT	865

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGAAGGTATATTGTTACTTACCAAATAACAAGTGTGGAAAG CAGGGAAAGCTCTTCAT <u>CCT</u> CACTAGATAAGTTCTCTTGAG GACTCTAATTCTGGCCCTCTCGGTAAACCTGA	866
	TCTAGTG <u>AGG</u> GATGAAGA	867
	TCTTCAT <u>CCT</u> CACTAGA	868
Breast Cancer Glu-1221-Stop GAA to TAA	GGTTACCGAAGAGGGCCAAGAAATTAGAGTCCTCAGAAGA GAACTTATCTAGTGAGGAT <u>GAAGAGCTCCCTGCTTCCAACA</u> CTTGTATTGGTAAAGTAACAAATACCTTCTCAGT	869
	ACTGAGAAGGTATATTGTTACTTACCAAATAACAAGTGTG GAAGCAGGGAAAGCT <u>CTTCATCCTCACTAGATAAGTTCTTC</u> TGAGGACTCTAATTCTGGCCCTCTCGGTAAACC	870
	GTGAGGAT <u>GAAGAGCTT</u>	871
	AAGCT <u>CTTCATCCTCAC</u>	872
Breast Cancer Glu-1250-Stop GAG to TAG	TTATTTGGTAAAGTAACAAATACCTTCTCAGTCTACTAGGC ATAGCACCGTTGCT <u>ACCGAGTGTCGTCTAAGAACACAGAGG</u> AGAATTATTATCATTGAAGAATAGCTAAATGACT	873
	AGTCATTAAAGCTATTCTCAATGATAAAATTCTCCTGTG TTCTTAGACAGACACT <u>CGGTAGCAACGGTGCTATGCCTAGTA</u> GACTGAGAAGGTATATTGTTACTTACCAAATAA	874
	TTGCTACCG <u>AGTGTC</u> GT	875
	CAGACACT <u>CGGTAGCAA</u>	876
Breast Cancer Ser-1262-Stop TCA to TAA	CTAGGCATAGCACCGTTGCTACCGAGTGTCGTCTAAGAACAA CAGAGGAGAATTATT <u>CATTGAAGAATAGCTAAATGACTG</u> CAGTAACCAGGTAATTGGCAAAGGCATCTCAGGA	877
	TCC TGAGATGCCTTGCCAATTACCTGGTTACTGCAGTCAT TTAAGCTATTCTCAAT <u>GATAATAAAATTCTCCTGTGTTCTTA</u> GACAGACACTCGGTAGCAACGGTGCTATGCCTAG	878
	TTTATTAT <u>CATTGAAGA</u>	879
	TCTTCAT <u>GATAATAAA</u>	880
10 Breast Cancer Gln-1281-Stop CAG to TAG	TTATCATTGAAGAATAGCTAAATGACTGCAGTAACCAGGTA TATTGGCAAAGGCAT <u>CTCAGGAACATCACCTTAGTGAGGAAA</u> CAAAATGTTCTGCTAGCTTGTGTTCTTCACAGTGCA	881
	TGCACGTGAGAAAACAAGCTAGCAGAACATTGTTCTC ACTAAGGTGATGTTCT <u>GAGATGCCATTGCAATATTACCTG</u> GTTACTGCAGTCATTAAAGCTATTCTCAATGATAA	882

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGGCATCT <u>CAGGAACAT</u>	883
	ATGTTCC <u>TGAGATGCCT</u>	884
Breast Cancer Gln-1313-Stop CAG to TAG	GCTAGCTTGTTCACAGTCAGTGAATTGGAAGACTTG ACTGCAAATACAAACACCC <u>CAGGATCCTTCTTGATTGGTCTT</u> CCAAACAAATGAGGCATCAGTCTGAAAGCCAGGGAG	885
	CTCCCTGGCTTCAGACTGATGCCTCATTTGTTGGAAGAAC CAATCAAGAAAGGATCCT <u>GGGTGTTGTATTGCACTGAA</u> CTTCCAATTCACTGCACTGTGAAGAAAACAAGCTAGC	886
	CAAACACCC <u>CAGGATCCT</u>	887
	AGGATCCT <u>GGGTGTTG</u>	888
Breast Cancer Ile-1318-Val ATT to GTT	TCACAGTCAGTGAATTGGAAGACTTGACTGCAAATACAAAC ACCCAGGATCCTTCTTGATTGGTCTCCAAACAAATGAGG CATCAGTCTGAAAGCCAGGGAGTTGGTCTGAGTGACA	889
	TGTCACTCAGACCAACTCCCTGGCTTCAGACTGATGCCTCA TTTGGTGAAGAACCAATCAAGAAAGGATCCTGGGTGTTG TATTGCAAGTCAAGTCTCCAATTCACTGCACTGTGA	890
	CTTCTTG <u>ATTGGTCT</u>	891
	AGAACCAATCAAGAAAG	892
Breast Cancer Gln-1323-Stop CAA to TAA	TTGGAAGACTTGACTGCAAATACAAACACCCAGGATCCTTC TTGATTGGTCTTCCAA <u>CAAATGAGGCATCAGTCTGAAAGC</u> CAGGGAGTTGGTCTGAGTGACAAGGAATTGGTTCAAG	893
	CTGAAACCAATTCCCTGTCACTCAGACCAACTCCCTGGCTT CAGACTGATGCCTCATTT <u>GTTGGAAGAACCAATCAAGAAAG</u> GATCCTGGGTGTTGATTGCAAGTCTTCAA	894
	CTTCCAA <u>CAAATGAGG</u>	895
	CCTCATTT <u>GTTGGAAAG</u>	896
10 Breast Cancer Arg-1347-Gly AGA to GGA	CAGTCTGAAAGCCAGGGAGTTGGTCTGAGTGACAAGGAATT GGTTTCAGATGATGAAGAA <u>AGAGGAACGGGCTTGAAGAAA</u> ATAATCAAGAAGAGCAAAGCATGGATTCAAACCTAGGTA	897
	TACCTAAGTTGAATCCATGCTTGCTCTTGTATTATTTCT TCCAAGCCC <u>GTTCCCTTCTTCTCATCATCTGAAACCAATTCT</u> TGTCACTCAGACCAACTCCCTGGCTTCAGACTG	898
	ATGAAGAA <u>AGAGGAACG</u>	899
	CGTTCC <u>TCTTCTTCTCAT</u>	900

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Gln-1395-Stop CAG to TAG	GAAACAAGCGTCTCTGAAGACTGCTCAGGGCTATCCTCTCAG AGTGACATTAAACCACT <u>CAGGTAAAAGCGTGTGTGTGT</u> GCACATGCGTGTGTGGTCCTTGCATTCACTAG	901
	CTACTGAATGCAAAGGACACCACACACACGCATGTGCACACA CACACACGCTTTACCT <u>GAGTGGTTAAATGTCAGTCTGAG</u> AGGATAGCCCTGAGCAGTCTCAGAGACGCTTGTTC	902
	TAACCACT <u>CAGGTAAA</u>	903
	TTTACCT <u>GAGTGGTTA</u>	904
Breast Cancer Gln-1408-Stop CAG to TAG	TGGTGCCATTATCGTTTGAAAGCAGAGGGATACCATGCAA CATAACCTGATAAAAGCT <u>CCAGCAGGAAATGGCTGAAC</u> TAGAA GCTGTGTTAGAACAGCATGGGAGCCAGCCTTCAACA	905
	TGTTAGAAGGCTGGCTCCATGCTGTTCAACACAGCTTCTA GTTCAGCCATTCTGCT <u>GGAGCTTATCAGGTTATGTTGCAT</u> GGTATCCCTGCTCAAAACGATAATGGCACCA	906
	TAAAGCT <u>CCAGCAGGAA</u>	907
	TTCCGT <u>GGAGCTTA</u>	908
Breast Cancer Arg-1443-Gly CGA to GGA Arg-1443-Stop CGA to TGA	AGCCAGCCTCTAACAGCTACCCCTCATCATAAGTGA CTGCCTTGAGGAC <u>CTGC</u> AAATCCAGAACAAAGCACATCA AAAAAGGTGTATTGTTGCCAAACACTGATATCT	909
	AGATATCAGTGTGGCCAACAATACACACCTTTCTGATGT GCTTGTTCTGGATT <u>TC</u> CGAGGTCTCAAGGGCAGAAGAGTC ACTTATGATGGAAGGGTAGCTGTTAGAAGGCTGGCT	910
	AGGAC <u>CTGC</u> AAATCCA	911
	TGGATT <u>TC</u> CGAGGTCT	912
	CAGAATAGAAACTACCCATCTCAAGAGGGAGCTATTAGGTT GTTGATGTGGAGGAGCAACAGCTGGAAAGAGTCTGGGCCACA CGATTGACGGAAACATCTTACTTGCCAAAGGCAAGATC	913
Breast Cancer Ser-1512-Ile AGT to ATT	GATCTTGCTTGGCAAGTAAGATGTTCCGTCAAATCGTGTG GCCCAGACTCTCAGCT <u>TTGCTC</u> CCACATCAACAAACCT TAATGAGCTCTTGTGAGATGGTAGTTCTATTCTG	914
	AGGAGCAAC <u>AGCTGGAA</u>	915
	TTCCAGCT <u>GTTGCTCCT</u>	916
	ATCTTCTAGGTCACTCCCTCTAAATGCCATCATTAGATGA TAGGTGGTACATGCACAGTTGCTCTGGGAGTCTTCAGAATAG AAACTACCCATCTCAAGAGGGAGCTATTAGTTG	917

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ACAACCTTAATGAGCTCCTTGTGAGATGGTAGTTCTATTCT GAAGACTCCCAGAGCA <u>ACT</u> TGTCATGTACCACCTATCATCTA ATGATGGGCATTTAGAAGGGGATGACCTAGAAAGAT	918
	CATGCACAC <u>G</u> TTGCTCTG	919
	CAGAGCA <u>ACT</u> TGTCATG	920
Breast Cancer Glu-1541-Stop GAG to TAG	CAGAATAGAAACTACCCATCTCAAGAGGAGCTCATTAAGGTT GTTGATGTGGAGGAGCA <u>A</u> CGCTGGAAGAGTCTGGGCCACA CGATTGACGGAAACATCTTACTTGCCAAGGCAAGATC	921
	GATCTTGCCTTGGCAAGTAAGATGTTCCGTCAAATCGTGTG GCCCGAGACTCTTCCAGCT <u>G</u> TTGCTCCTCCACATCAACAAACCT TAATGAGCTCCTTGTGAGATGGTAGTTCTATTCTG	922
	AGGAGCA <u>A</u> CGCTGGAA	923
	TTCCAGCT <u>G</u> TTGCTCCT	924
Breast Cancer Thr-1561-Ile ACC to ATC	AACTACCCATCTCAAGAGGAGCTCATTAAGGTTGTTGATGTG GAGGAGCAACAGCTGGAAGAGTCTGGGCCACACGATTGAC GGAAACATCTTACTTGCCAAGGCAAGATCTAGGTAATA	925
	TATTACCTAGATCTTGCCTTGGCAAGTAAGATGTTCCGTCAA ATCGTGTGGCCCAGACT <u>C</u> TTCCAGCTGTTGCTCCTCCACATC AACAAACCTTAATGAGCTCCTTGTGAGATGGTAGTT	926
	AGCTGGAAGAGTCTGGG	927
	CCCAGACTCTTCCAGCT	928
Breast Cancer Tyr-1563-Stop TAC to TAG	TTTGTAAATTCAACATTATCGTTGTAAATTAAACTTCTCCCA TTCTTTCAGAGGG <u>A</u> CCCCTTACCTGGAATCTGGAATCAGC CTCTTCTGTGATGACCCTGAATCTGATCCTCTGA	929
	TCAGAAGGATCAGATTCAAGGGTCATCAGAGAAGAGGCTGATT CCAGATTCCAGGTAAAGGG <u>G</u> TTCCCTCTGAAAGGAATGGGAG AAGTTTAATTACACAAACGATGAATGTTGAATTACAAA	930
	AGAGGG <u>A</u> CCCCTTACC	931
	GGTAAGGG <u>G</u> TTCCCTCT	932
10 Breast Cancer Leu-1564-Pro CTG to CCG	CAACATTATCGTTGTAAATTAAACTTCTCCATTCTTC AGAGGG <u>A</u> CCCCTTACCTGGAATCTGGAATCAGCCTCTTC TGATGACCCTGAATCTGATCCTCTGAAGACAGAGC	933
	GCTCTGTCTTCAGAAGGGATCAGATTCAAGGG <u>I</u> CATCAGAGAAG AGGCTGATTCCAGATT <u>C</u> AGGTAAAGGG <u>G</u> TTCCCTCTGAAAG GAATGGGAGAAGTTAATTACACAAACGATGAATGTTG	934

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:	
	CCCTTACCTGGAATCTG	935	
	CAGATTCCAGGTAAAGGG	936	
Breast Cancer Gln-1604-Stop CAA to TAA	GCCCCAGAGTCAGCTCGTGGCAACATACCATCTTCACC TCTGCATTGAAAGTTCCC <u>A</u> TTGAAAGTTGCAGAACATGCC CAGAGTCCAGCTGCTCATACTACTGTACTGCTG	937	
	CAGCAGTATCAGTAGTATGAGCAGCAGCTGGACTCTGGCA GATTCTGCAACTTCAATT <u>G</u> GGGAAC <u>T</u> TCATGCAGAGGTT GAAGATGGATGTTGCCAACACGAGCTGACTCTGGGC	938	
	AAGTTCCC <u>A</u> TTGAAA	939	
	TTTC <u>A</u> TT <u>G</u> GGGAAC <u>T</u> T	940	
Breast Cancer Lys-1606-Glu AAA to GAA	GAGTCAGCTCGTGGCAACATACCATCTTCAC <u>C</u> CTTGCA TTGAAAGTTCCC <u>A</u> TT <u>G</u> AAAGTTGCAGAACATGCCAGAGT CCAGCTGCTCATACTACTGTACTGCTGGGTATA	941	
	TATACCCAGCAGTATCAGTAGTATGAGCAGCAGCTGGACTCT GGGCAGATTCTGCAACTT <u>I</u> CAATTGGGAAC <u>T</u> TCATGCAG AGGTTGAAGATGGATGTTGCCAACACGAGCTGACTC	942	
	CCCAATT <u>G</u> AAAGTTGCA	943	
	TGCAACTT <u>I</u> CAATTGGG	944	
Breast Cancer Met-1628-Thr ATG to ACG	CAGAATCTGCCAGAGTCAGCTGCTCATACTACTGTATA CTGCTGGGTATAAT <u>G</u> CA <u>I</u> GGAAAGAAAGTGTGAGCAGGGAG AAGCCAGAATTGACAGCTCAACAGAAAGGGTCAACAA	945	
	TTGTTGACCC <u>T</u> CTGTTGAAGCTGTCAATTCTGGCTTCTCCC TGCTCACACTTCT <u>C</u> <u>A</u> TTGCATTATA <u>CC</u> CAGCAGTACAGT AGTATGAGCAGCAGCTGGACTCTGGCAGATTCTG	946	
	TAAT <u>G</u> CA <u>A</u> GGAAAGAAA	947	
	TTT <u>C</u> <u>T</u> <u>C</u> <u>C</u> <u>A</u> TTGCATTA	948	
10	Breast Cancer Met-1628-Val ATG to GTG	GCAGAATCTGCCAGAGTCAGCTGCTCATACTACTGTATA ACTGCTGGGTATAAT <u>G</u> CA <u>A</u> GGAAAGAAAGTGTGAGCAGGGAG GAAGCCAGAATTGACAGCTCAACAGAAAGGGTCAACAA	949
	TGTTGACCC <u>T</u> CTGTTGAAGCTGTCAATTCTGGCTTCTCCC GCTCACACTTCT <u>C</u> <u>A</u> TTGCATTATA <u>CC</u> CAGCAGTACAGT GTATGAGCAGCAGCTGGACTCTGGCAGATTCTG	950	
	ATAAT <u>G</u> CA <u>A</u> GGAAAGAAA	951	

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTCTTCCATTGCATTAT	952
Breast Cancer Pro-1637-Leu CCA to CTA	CTCATACTACTGATACTGCTGGGTATAATGCAATGGAAGAAA GTGTGAGCAGGGAGAAG <u>CCAGAATTGACAGCTTCACAGAA</u> AGGGTCAACAAAAGAATGTCATGGTGGTGTCTGGCCT	953
	AGGCCAGACACCACCATGGACATTCTTGTGACCCTTCT GTTGAAGCTGTCAATTCT <u>GGCTCTCCCTGCTCACACTTCTT</u> CCATTGCATTATACCCAGCAGTATCAGTAGTATGAG	954
	GGAGAAG <u>CCAGAATTGA</u>	955
	TCAATTCT <u>GGCTTCTCC</u>	956
Breast Cancer Met-1652-Ile ATG to ATA	GAGCAGGGAGAAG <u>CCAGAATTGACAGCTCAACAGAAAGGG</u> TCAACAAAAGAATGTC <u>CCATGGTGGTGTCTGGCCTGACCCCAG</u> AAGAATTGAGTGTATCCATATGTATCTCCCTAATG	957
	CATTAGGGAGATACATATGGATA <u>CACTCACAAATTCTTCTGG</u> GGTCAGGCCAGACACC <u>ACCATGGACATTCTTGTGACCCCT</u> TTCTGTTGAAGCTGTCAATTCTGGCTCTCCCTGCTC	958
	ATGTC <u>CCATGGTGGTGT</u> C	959
	GACACC <u>ACCATGGACAT</u>	960
Breast Cancer Glu-1694-Stop GAG to TAG	CACTTCCTGATTTGTTCAACTCTAATCCTTGAGTGT TCATTCTGCAGATG <u>CTGAGTTGTGTGAACGGACACTGAA</u> ATATTTCTAGGAATT <u>GCAGGAGGAAATGGTAG</u>	961
	CTACCCATTTC <u>CTCCCGCAATTCTAGAAAATATTCAGTGT</u> CCGTCACACACAA <u>ACTCAGCATCTGCAGAATGAAAAACACT</u> CAAAGGATTAGAAG <u>TTGAAACAAAATCAGGAAGTG</u>	962
	CAGATG <u>CTGAGTTGTG</u>	963
	CACAA <u>ACTCAGCATCTG</u>	964
10 Breast Cancer Gly-1706-Glu GGA to GAA	GTGTTTT <u>CATTCTGCAGATGCTGAGTTGTGTGAACGG</u> CACTGAA <u>ATATTCTAGGAATTGCAGGAGGAAATGGTAG</u> TTAGCTATTCTGTAAGTATA <u>ACTATTCTCCCT</u>	965
	AGGGGAGAA <u>ATAGTATTACTACAGAAATAGCTAACTACCC</u> ATTT <u>CCTCCCGCAATTCTAGAAAATATTCAGTGTCCGTT</u> ACACACAA <u>ACTCAGCATCTGCAGAATGAAAAACAC</u>	966
	TTTT <u>CTAGGAATTGCAGG</u>	967
	CCGCAATT <u>CCTAGAAAA</u>	968

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Ala-1708-Glu GCG to GAG	TTCAATTCTGCAGATGCTGAGTTGTGTGAACGGACACTGA AATATTTCTAGGAATT <u>GCGGGAGGAAAATGGGTAGTTAGCT</u> ATTCTGTAAGTATAAACTATTCTCCCTCCTCCC	969
	GGGAGGAGGGAGAAATAGTATTATACTTACAGAAATAGCTA ACTACCCATTTCCTCCCGCAATTCTAGAAAATATTTCAGTG TCCGTTCACACACAAACTCAGCATCTGCAGAATGAA	970
	AGGAATT <u>GCGGGAGGAA</u>	971
	TTCCCTCCCGCAATTCT	972
Breast Cancer Val-1713-Ala GTA to GCA	CTGAGTTGTGTGAACGGACACTGAAATATTCTAGGAAT TGCAGGGAGGAAAATGGGTAGTTAGCTATTCTGTAAGTATAA TACTATTCTCCCTCCCTTAAACACCTCAGAA	973
	TTCTGAGGTGTTAAAGGGAGGGAGGGAGAAATAGTATTATAC TTACAGAAATAGCTAACT <u>ACCCATTTCCTCCCGCAATTCTA</u> GAAAATATTCAAGTGTCCGTTCACACACAAACTCAG	974
	AAAATGGGTAGTTAGCT	975
	AGCTAACT <u>ACCCATTTC</u>	976
Breast Cancer Trp-1718-Stop TGG to TAG	AACGGACACTGAAATATTCTAGGAATT <u>GCGGGAGGAAAAT</u> GGGTAGTTAGCTATTCT <u>GTAAGTATAAACTATTCTCCCT</u> CCTCCCTTAAACACCTCAGAAATTGCATTTCACACC	977
	GGTGTAAAATGCAATTCTGAGGTGTTAAAGGGAGGGAGGG AGAAATAGTATTATACTT <u>ACAGAAATAGCTAACTACCCATTTC</u> CTCCCGCAATTCTAGAAAATATTCAAGTGTCCGTT	978
	CTATTCT <u>GTAAGTATA</u>	979
	TATACTT <u>ACAGAAATAG</u>	980
10 Breast Cancer Glu-1725-Stop GAA to TAA	TTCTGCTGTATGTAACCTGTCTTCTATGATCTCTTAGGGG TGACCCAGTCTATTAA <u>AGAAAGAAAATGCTGAATGAGGTA</u> GTACTTGATGTTACAAACTAACCAAGAGATATTCTT	981
	AATGAATATCTGGTAGTTGTAACATCAAGTACCTACCTC ATTCA <u>GCATTTCCTTAAATAGACTGGGTACCCCTAA</u> GAGATCATAGAAAAGACAGGGTACATACAGCAGAA	982
	CTATTAA <u>AGAAAGAAA</u>	983
	TTTCTT <u>CTTAAATAG</u>	984
15 Breast Cancer Lys-1727-Stop AAA to TAA	TGTATGTAACCTGTCTTCTATGATCTCTTAGGGTGACCC AGTCTATTAA <u>AGAAAGAAAATGCTGAATGAGGTAAGTACTTG</u> ATGTTACAAACTAACCAAGAGATATTCAATTCA	985

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TGACTGAATGAATATCTCTGGTTAGTTGTAACATCAAGTACT TACCTCATTCAAGCATTTTCTTTCTTAATAGACTGGTCACC CCTAAAGAGATCATAGAAAAGACAGGTTACATACA	986
	AAGAAAGAAAAATGCTG	987
	CAGCATTTCCTTCTT	988
Breast Cancer Pro-1749-Arg CCA to CGA	TCTTCAGCATGATTGAAGTCAGAGGGAGATGTGGTCAATG GAAGAAACCACCAAGGT <u>CCAAAGCGAGCAAGAGAATCCCAG</u> GACAGAAAGGTAAAGCTCCCTCCCTCAAGTTGACAAAAA	989
	TTTGTCAACTTGAGGGAGGGAGCTTACCTTCTGTCTGG GATTCTCTTGCTCGCTT <u>G</u> ACCTGGTGGTTCTCCATTGA CCACATCTCCTCTGACTTCAAAATCATGCTGAAAGA	990
	CCAAGGT <u>CCAAAGCGAG</u>	991
	CTCGCTT <u>G</u> ACCTGG	992
	CAGCATGATTGAAGTCAGAGGGAGATGTGGTCAATGGAAGA AACCAACCAAGGT <u>CCAAAGCGAGCAAGAGAATCCCAGGACAG</u> AAAGGTAAAGCTCCCTCCCTCAAGTTGACAAAAATCTC	993
Breast Cancer Arg-1751-Stop CGA to TGA	GAGATTTTGTCACCTGAGGGAGGGAGCTTACCTTCTGT CCTGGGATTCTCTTGCTCG <u>CTTGGACCTGGTGGTTCTC</u> CATTGACCACATCTCCTCTGACTTCAAAATCATGCTG	994
	GTCCAAAG <u>CGAGCAAGA</u>	995
	TCTTGCTCG <u>CTTGGAC</u>	996
	GTCAGAGGGAGATGTGGTCAATGGAAGAAACCACCAAGGT <u>CC</u> AAAGCGAGCAAGAGAAT <u>CCCAGGACAGAAAGGTAAAGCTCC</u> CTCCCTCAAGTTGACAAAAATCTCACCCCCACCACACTGT	997
	ACAGAGTGGTGGGGTGAGATTTTGTCACCTGAGGGAGGG AGCTTACCTTCTGT <u>CGCTTGGATTCTTGTGCTCGCTTGG</u> CCTTGGTGGTTCTCCATTGACCACATCTCCTCTGAC	998
Breast Cancer Gln-1756-Stop CAG to TAG	GAGAAT <u>CCCAGGACAGA</u>	999
	TCTGT <u>CGCTTGGATTCTC</u>	1000
	CTCTCTTCTCCAGATCTCAGGGGGTAGAAATCTGTGCT ATGGGCCCTTCACCAACAT <u>GCC</u> CACAGGTAAAGAGCCTGGGA GAACCCCCAGAGTTCCAGCACCAGCCTTGTCTTACATA	1001
	TATGTAAGACAAAGGCTGGTGTGGAACTCTGGGGTTCTCCC AGGCTCTACCTGTGG <u>CAT</u> GTTGGTGAAGGGCCCAGAGCA ACAGATTCTAGCCCCCTGAAGATCTGGAAGAAGAGAG	1002

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:	
	CACCAACATGCCACAG	1003	
	CTGTGGCATGTTGGT	1004	
Breast Cancer Trp-1782-Stop TGG to TGA	AGTATGCAGATTACTGCAGTGATTTACATCTAAATGTCCATT TTAGATCACTGGAAT <u>GG</u> ATGGTACAGCTGTGTTGCTTCT GTGGTGAAGGAGCTTCATCATTACCCTGGCACA	1005	
	TGTCCAAGGGTGAATGATGAAAGCTCCTCACACAGAAC ACCACACAGCTGTACCAT <u>CC</u> ATTCCAGTTGATCTAAATGGA CATTAGATGTAAAATCACTGCAGTAATCTGCATACT	1006	
	CTGGAAT <u>GG</u> ATGGTACA	1007	
	TGTACCAT <u>CC</u> ATTCCAG	1008	
Breast Cancer Gln-1785-His CAG to CAT	ATTACTGCAGTGATTTACATCTAAATGTCCATTAGATCAAC TGGAATGGATGGTACAG <u>CT</u> GTTGTTGCTTGTGGTGAAG GAGCTTCATCATTACCCTGGCACAGTAAGTATT	1009	
	AATACTTACTGTGCCAAGGGTGAATGATGAAAGCTCCTTCAC CACAGAACGACCACACAG <u>CT</u> TACCATCCATTCCAGTTGATC TAAAATGGACATTAGATGTAAAATCACTGCAGTAAT	1010	
	ATGGTACAG <u>CT</u> GTTGG	1011	
	CCACACAG <u>CT</u> TACCAT	1012	
Breast Cancer Glu-1794-Asp GAG to GAT	GTCCATTAGATCAACTGGAATGGATGGTACAGCTGTGTTG TGCTTCTGTGGTGAAGGAG <u>CT</u> TTCATCATTACCCTGGCAC AGTAAGTATTGGGTGCCCTGTCAGAGAGGGAGGACAC	1013	
	GTGTCCTCCCTCTGACAGGGCACCAACTTACTGTGCC AAGGGTGAATGATGAAAG <u>CT</u> CCTTCACCACAGAACACCACA CAGCTGTACCATCCATTCCAGTTGATCTAAATGGAC	1014	
	GTGAAGGAG <u>CT</u> TTCATC	1015	
	GATGAAAG <u>CT</u> CCTTCAC	1016	
10	Breast Cancer Arg-1835-Stop CGA to TGA	CTCTGCTTGTGTTCTGTCTCCAGCAATTGGGAGATGTG GAGGCACCTGTGGTACCC <u>G</u> AGAGTGGGTGTTGGACAGTGT AGCACTCTACCAAGTGCCAGGAGCTGGACACCTACCTGA	1017
	TCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAGTGCTACA CTGTCCAACACCCACTCT <u>GG</u> TCACCACAGGTGCCTCACA CATCTGCCCAATTGCTGGAGACAGAGAACACAAGCAGAG	1018	
	TGGTGACCC <u>G</u> AGAGTGG	1019	
	CCACTCTCGGGTCACCA	1020	

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast Cancer Trp-1837-Arg TGG to CGG	TTGTGTTCTCTGTCTCCAGCAATTGGGCAGATGTGTGAGGCA CCTGTGGTGACCCGAGAG <u>T</u> GGGTGTTGGACAGTGTAGCACT CTACCAGTGCCAGGAGCTGGACACCTACCTGATAACCCC	1021
	GGGGTATCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAGT GCTACACTGTCCAACACCC <u>A</u> CTCTCGGGTCACCACAGGTGC CTCACACATCTGCCCAATTGCTGGAGACAGAGAACACAA	1022
	CCCGAGAG <u>T</u> GGGTGTTG	1023
	CAACACCC <u>A</u> CTCTCGGG	1024
Breast Cancer Trp-1837-Stop TGG to TAG	TGTGTTCTCTGTCTCCAGCAATTGGGCAGATGTGTGAGGCAC CTGTGGTGACCCGAGAG <u>T</u> GGGTGTTGGACAGTGTAGCACTC TACCACTGCCAGGAGCTGGACACCTACCTGATAACCCC	1025
	TGGGTATCAGGTAGGTGTCCAGCTCCTGGCACTGGTAGAG TGCTACACTGTCCAACACCC <u>A</u> CTCTCGGGTCACCACAGGTG CCTCACACATCTGCCCAATTGCTGGAGACAGAGAACACA	1026
	CCGAGAG <u>T</u> GGGTGTTGG	1027
	CCAACACCC <u>A</u> CTCTCGG	1028

Table 15
BRCA2 Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer PHE32LEU TTT to CTT	GTTAAAACAAGGTGGATTTTTTTAAATAGATTAGGAC CAATAAGTCTTAATTGG <u>T</u> GAAGAACTTCTTCAGAAGCTCC ACCCTATAATTCTGAACCTGCAGAAGAATCTGAAC	1029
	GTTCAGATTCTCTGCAGGTTCAGAATTATAGGGTGGAGCTT CTGAAGAAAGTTCTCAA <u>ACCA</u> ATTAAAGACTTATTGGTCCTAA ATCTATTAAAAAAAATCCCACCTTAGTTAAC	1030
	TTAATTGG <u>T</u> GAAGAA	1031
	TTCTTCAA <u>ACCA</u> ATTAA	1032
Breast cancer TYR42CYS TAT to TGT	TAGATTAGGACCAATAAGTCTTAATTGGTTGAAGAACTTTC TTCAGAAGCTCCACCC <u>T</u> TAATTCTGAACCTGCAGAAGAATC TGAACATAAAAACAACAATTACGAACCAAACCTATT	1033

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AATAGGTTGGTCGAATTGTTGTTTATGTTAGCTCAGATTCTTC TGCAGGTTCAGAATT <u>TAGGGTGGAGCTCTGAAGAAAGTTC</u> TTCAAACCAATTAAAGACTTATTGGTCCTAAATCTA	1034
	TCCACC <u>CTATAATTCTG</u>	1035
	CAGAATT <u>TAGGGTGGA</u>	1036
Breast cancer LYS53ARG AAA to AGA	AAGAAC <u>TTCTCAGAAGCTCCACCC</u> TATAATTCTGAACCTGC AGAAGAAC <u>CTGAACATAAAAACAACAATTACGAACCAAACCTA</u> TTTAA <u>AACTCCACAAAGGAAACC</u> ATCTTATAATCA	1037
	TGATTATAAGATGGTTCTTGTGGAGTTAA <u>TAGGTTG</u> GTTCGTA <u>ATTGTTGTTT</u> ATGTT <u>CAGATTCTCTGCAGGTC</u> AGAATT <u>TAGGGTGGAGCTCTGAAGAAAGTTCT</u>	1038
	TGAAC <u>CATAAAAACAACA</u>	1039
	TGTTG <u>TTT</u> ATGTTCA	1040
	CTATTTAA <u>ACTCCACAAAGGAAACC</u> ATCTTATAATCAGCTGG CTTCA <u>ACTCCAATAAAT</u> AT <u>CAAGAGCAAGGGCTGACTCTGC</u> CGCTGT <u>ACCAATCTCCTGTAA</u> AGAATTAGATAAAAT	1041
Breast cancer Phe81Leu TTC to CTC	ATTTATCTAATT <u>CTTACAGGAGATTGGTACAGCGGCAGAGT</u> CAGCC <u>CTTGCTCTTGA</u> ATATTATTGGAGTTGAAGCCAGCTG ATTATAAGATGGTT <u>CTTGTGGAGTTAA</u> ATAG	1042
	CAATA <u>ATTA</u> CAAGAG	1043
	CT <u>CTTGA</u> ATATTATTG	1044
	GTCAGAC <u>ACCAAAACATATTCTGAAAGTCTAGGAGCTGAGG</u> TGGAT <u>CCTGATATGTCTT</u> <u>GGTCAAGTCTT</u> AGCTACACCACC CAC <u>CCCTAGTTCTACTGTGCTCATAGG</u> TAATAATAG	1045
Breast cancer TRP194TERM TGG to TAG	CTATTATTAC <u>CTATGAGCACAGTAGAA</u> CTAAGGGTGGGTGGT GTAG <u>CTAAAGAACTTGACCAAGAC</u> ATATCAGGATCCACCTCA GCT <u>CCTAGACTTCAGAA</u> ATATGTTGGTGTCTGAC	1046
	TATG <u>TCTTGGTCAAGTT</u>	1047
	AA <u>CTTGACCAAGACATA</u>	1048
	CTGAAAGT <u>CTAGGAGCTGAGGTGGATCCTGATATGTCTGGT</u> CAAG <u>TTCTT</u> AG <u>CTACACCACCCACCC</u> TTAG <u>TTCTACTGTGCT</u> CAT <u>AGGTAATAATAGCAAATGTG</u> TATTACAAGAAA	1049
10 Breast cancer PRO201ARG CCA to CGA	TTT <u>CTTGAAATACACATTGCTATT</u> TTAC <u>CTATGAGCACAGT</u> AGAA <u>CTAAGGGTGGGTGGT</u> AG <u>CTAAAGAACTTGACCAAGA</u> CAT <u>ATCAGGATCCACCTCAGCTC</u> AG <u>ACTTCA</u>	1050

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGCTACACCACCCACCC	1051
	GGGTGGGTGGTAGCT	1052
Breast cancer Pro222Ser CCT to TCT	ACAATACACATAAATTATCTTACAGTCAGAAATGAAGAAG CATCTGAAACTGTATTC <u>CCT</u> CATGATACTACTGCTGTAAGTAA ATATGACATTGATTAGACTGTTGAAATTGCTAAC	1053
	TGTTAGCAATTCAACAGTCTAATCAATGTCATATTACTTACA GCAGTAGTATCATGAG <u>GAA</u> ATACAGTTTCAGATGCTTCTTCAT TTCTGACTGTAAGATAAAAATTATGTGTATTGT	1054
	CTGTATTC <u>CCT</u> CATGAT	1055
	ATCATGAG <u>GAA</u> ATACAG	1056
Breast cancer Leu-414-Term TTG to TAG	AATGGTCTCAACTAACCCCTTCAGGTCTAAATGGAGGCCAGA TGGAGAAAATACCCCTATT <u>GC</u> ATATTCTTCATGTGACCAAAA TATTTCAGAAAAAGACCTATTAGACACAGAGAACAA	1057
	TTGTTCTCTGTCTAATAGGTCTTTCTGAAATATTGGTC ACATGAAGAAAAT <u>GC</u> AATAGGGTATTCTCCATCTGGC TCCATTAGACCTGAAAGGGTAGTTGAGACCATT	1058
	ACCCCTATT <u>GC</u> ATATT	1059
	AAATAT <u>GC</u> AATAGGGT	1060
Breast cancer, male Cys554Trp TGT to TGG	AGCCTCTGAAAGTGGACTGGAATACATACTGTTGCTCACA GAAGGAGGACTCCTTAT <u>GT</u> <u>CCA</u> ATTAAATTGATAATGGAAG CTGGCCAGCCACCACACAGAATTCTGTAGCTTG	1061
	CAAAGCTACAGAATTCTGTGGTGGCTGGCAGCTC CATTATCAATTAAATTGG <u>AC</u> ATAAGGAGTCCTCCTCTGTGA GAAACAGTATGTATTCCAGTCCACTTCAGAGGCT	1062
	TCCTTAT <u>GT</u> <u>CCA</u> ATT	1063
	AAATTGG <u>AC</u> ATAAGGA	1064
10 Breast cancer Lys944Term AAA to TAA	AACTCTACCATGGTTTATATGGAGACACAGGTGATAAACAA GCAACCCAA <u>GT</u> TCATT <u>AAAAAAG</u> ATTGGTTATGTTCTG CAGAGGAGAACAAAATAGTGTAAAGCAGCATATAA	1065
	TTATATGCTGCTTACACTATTGTTCTCTCTGCAAGAAC ATAAACCAATCTTT <u>TA</u> ATTGACACTGGGTTGCTTGTATT CACCTGTGTCTCCATATAAACCATGGTAGAGTT	1066
	TGTCAATT <u>AAAAAAG</u> AT	1067
	ATCTTT <u>TA</u> ATTGACA	1068

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer, male Glu1320Term GAA to TAA	ATGACTACTGGCACTTTGTTGAAGAAATTACTGAAAATTACA AGAGAAATACTGAAAAT <u>G</u> AAGATAACAAATATACTGCTGCCAG TAGAAATTCTCATACTAGAATTGATGGCAGTG	1069
	CACTGCCATCAAATTCTAAGTTATGAGAATTCTACTGGCAGC AGTATATTGTTATCTT <u>C</u> ATTTCACTGTTCTCTGTAAATTTC AGTAATTCTTCAACAAAAGTGCCAGTAGTCAT	1070
	CTGAAAAT <u>G</u> AAGATAAC	1071
	GTTATCTT <u>C</u> ATTTCA	1072
Breast cancer Glu1876Term GAA to TAA	CATGAAACAAATTAAAAAGTGAAGACATATTACAGACAGTT TCAGTAAAGTAATTAAGGAAAACAACGAGAATAAATCAAAAAT TTGCCAACGAAAATTATGGCAGGTTGTTACGAGG	1073
	CCTCGTAACAACCTGCCATAATTTCGTTGGCAAATTGAA TTTATTCTCGTTGTT <u>C</u> TTAATTACTTACTGAAACTGTCTG TAAATATGTCTTCACTTTTAATTGTTCATG	1074
	TAATTAA <u>G</u> AAAACAAC	1075
	GTTGTTT <u>C</u> TTAATT	1076
Breast cancer Ser1882Term TCA to TAA	TGAAAGACATATTACAGACAGTTCA <u>G</u> TAAGTAATTAAAGGA AAACAACGAGAATAAAT <u>C</u> AAAAATTGCCAACGAAAATTATG GCAGGTTGTTACGAGGCATTGGATGATTAGAGGA	1077
	TCCTCTGAATCATCCAATGCCCGTAACAAACCTGCCATAATT TCGTTGGCAAATT <u>T</u> <u>G</u> ATTATTCTCGTTGTTCTTAATT ACTTACTGAAACTGTCTGTAAATATGTCTTCA	1078
	GAATAAA <u>C</u> AAAATT	1079
	AAATT <u>T</u> <u>T</u> <u>T</u> <u>G</u> ATTATT	1080
10 Breast cancer Glu1953Term GAA to TAA	AACCAAAATATGTCTGGATTGGAGAAAGTTCTAAATATCAC CTTGTGATGTTAGTTGGAAACTTCAGATATATGTAAATGTAG TATAGGGAAGCTTCATAAGTCAGTCTCATCTGCAA	1081
	TTGCAGATGAGACTGACTTATGAAGCTCCCTACTACATT ACATATATCTGAAGTT <u>C</u> CAAACAAACATCACAAAGGTGATATT TTAGAAACTTCTCCAATCCAGACATATTGGTT	1082
	TTAGTT <u>G</u> AAACTTCA	1083
	TGAAGTT <u>C</u> AAACTAA	1084
15 Breast cancer Ser1970Term TCA to TAA	TTAGTTGGAAACTTCAGATATATGTAAATGTAGTATAGGGAA GCTTCATAAGTCAGTCT <u>C</u> ATCTGCAAATACTTGTGGGATT AGCACAGCAAGTGGAAAATCTGTCCAGGTATCAGA	1085

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCTGATACCTGGACAGATTTCACTTGCTGTGCTAAAAATCC CACAAGTATTGCAGAT <u>GAGACTGACTTATGAAGCTTCCCTAT</u> ACTACATTACATATATCTGAAGTTCCAAACTAA	1086
	GTCAGTCT <u>CATCTGCAA</u>	1087
	TTGCAGAT <u>GAGACTGAC</u>	1088
Breast cancer Gln1987Term CAG to TAG	AAGTCAGTCTCATCTGCAAATACTTGTGGGATTTAGCACAG CAAGTGGAAAATCTGT <u>CCAGGTATCAGATGCTTCATTACAAA</u> CGCAAGACAAGTGT <u>TTCTGAAATAGAAGATAGTA</u>	1089
	TACTATCTTCTATTTCAGAAAACACTTGTCTTGCCTTTGTAAT GAAGCATCTGATA <u>CTGACAGATTTCACTTGCTGTGCTA</u> AAAATCCCACAAGTATTGCAGATGAGACTGACTT	1090
	AATCTGT <u>CCAGGTATCA</u>	1091
	TGATACCT <u>GGACAGATT</u>	1092
Breast cancer Ala2466Val GCA to GTA	AAAATAAGATTAATGACAATGAGATT <u>CATCAGTTAACAAAAA</u> CAACTCCAATCAAGCAG <u>CAGCTGTAACTTCAAAAGTGTGA</u> AGAAGAAC <u>CTTAGGTATTGTATGACAATTGTGTG</u>	1093
	CACACAAATTGT <u>CATACAATAACCTAAAGGTTCTTCTTCACACT</u> TTGTGAAAGTTACAGCT <u>GCTGCTGATTGGAGTTTTGTT</u> AAACTGATGAAT <u>CTCATTGTCTTAATCTTATT</u>	1094
	TCAAGCAG <u>UAGCTGTAA</u>	1095
	TTACAGCT <u>GCTGCTTGA</u>	1096
10 Breast cancer Arg2520Term CGA to TGA	AGGCAACGCGTCTTCCACAGCCAGGCAGTCTGTATCTGCA AAAACATCCACTCTGCCT <u>CGAATCTCTGTAAAGCAGCAGTA</u> GGAGGCCAAGTCCCCT <u>CTGCGTGTCCCTATAAACAGG</u>	1097
	CCTGTTATGAGGACACGCAGAGGGACTTGGCCTCCTACT GCTGCTT <u>CAGAGAGATTGAGGCAGAGTGGATGTTTGCA</u> AGATACAGACTGCCTGGCTGTGGAAAGACGC <u>GTGCTGCCT</u>	1098
	CTCTGCCT <u>CGAATCTCT</u>	1099
	AGAGATT <u>CGAGGCAGAG</u>	1100
Breast cancer Gln2714Term CAA to TAA	ATTCATTGAGCGCAAATATCTGAAACTTCTAGCAATAAAA CTAGTAGTGCAGATACC <u>CAAAAGTGGCCATTATTGAACCTA</u> CAGATGGGTGGTATGCT <u>GTAAAGGCCAGTTAGATC</u>	1101
	GATCTAACTGGGC <u>CTTAACAGCATAACCACCCATCTGTAAGTT</u> CAATA <u>ATGGCCACTTTTGGTATCTGCACTACTAGTTTATT</u> GCTAGAAGTT <u>CAGATATATTGCGCTCAATGAAAT</u>	1102

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CAGATACCCAAAAAGTG	1103
	CACTTTTGGTATCTG	1104
Breast cancer Leu2776Term TTA to TGA	CAGAACTGGTGGGCCTCCTGATGCCGTACACCTCTGAAG CCCCAGAACATCTCTTATGTTAAAGGTAATTAAATTGCACTCTT GGTAAAATCAGTCATTGATTCAAGTAAATTCTAGA	1105
	TCTAGAATTAACTGAATCAATGACTGATTTACCAAGAGTG CAAATTAATTACCTTAAACATAAGAGATTCTGGGGCTTCAAG AGGTGTACAGGCATCAGGAGAGCCCACCAGTCTG	1106
	TCTTATGTTAAAGATT	1107
	AAATCTTAAACATAAGA	1108
Breast cancer Gln2893Term CAG to TAG	CCTTTGTTCTTAGAAAACACAACAAAACCATTACCATC ACGTGCACAAAGACAGCAAGTCTGCTTCAAGATGG TGCAGAGCTTATGAAGCAGTGAAGAATGCAGCAG	1109
	CTGCTGCATTCTTCACTGCTTCATAAAGCTCTGCACCACCTTG CAAAGCACGAACCTGCTGTCTGTTAGTCACGTGATGGTAA ATATGGTTTGTGTGTTCTAAGAAAACAAAAGG	1110
	TAACAAGACAGCAAGTT	1111
	AACTTGCTGTCTGTTA	1112
Breast cancer Ala2951Thr GCC to ACC	AATCACAGGCAAATGTTGAATGATAAGAAACAAGCTCAGATC CAGTGGAAATTAGGAAGGCCATGGAATCTGCTGAACAAAAG GAACAAGGTTTATCAAGGGATGTACAACCGTGTGGA	1113
	TCCACACGGTTGTGACATCCCTGATAAACCTGTTCTTGTG TTCAGCAGATTCCATGGCCTTCTTAATTCCAACGGATCTGA GCTTGTCTTATCATTCAACATTGCTGTGATT	1114
	TTAGGAAGGCCATGGAA	1115
	TTCCATGGCCTTCTAA	1116
10 Breast cancer Met3118Thr ATG to ACG	ACAATTACTGGCAATAAAGTTGGATAGACCTTAATGAGGA CATTATTAAGCCTCATATGTTAATTGCTGCAAGCAACCTCCAG TGGCGACCAGAACATCAAATCAGGCCTTCTACTT	1117
	AAAGTAAGAAGGCCTGATTGGATTCTGGTCGCCACTGGAG GTTGCTTGCAGCAATTAAACATATGAGGCTTAATAATGTCCTCA TTAAGGTCTATCCAAAACTTATTGCCAGTAAATTGT	1118
	GCCTCATATGTTAATTG	1119
	CAATTAACATATGAGGC	1120

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Breast cancer Thr3401Met ACG to ATG	GACTGAAACGACGTTGTACTACATCTCTGATCAAAGAACAGG AGAGTTCCCAGGCCAGTAC <u>CG</u> GAAGAATGTGAGAAAAATAAGC AGGACACAATTACAACATAAAAATATCTAACGCTT	1121
	AATGCTTAGATATATTTTGTAGTTGTAATTGTGTCTGCTTATT TTTCTCACATTCTTCC <u>G</u> TACTGGCCTGGGAACCTCCTGTTCT TTGATCAGAGATGTAGTACAACGTCGTTAGTC	1122
	GGCCAGTAC <u>CG</u> GAAGAAT	1123
	ATTCTTCC <u>G</u> TACTGGCC	1124
Breast cancer Ile3412Val ATT to GTT	AAAGAACAGGAGAGTTCCCAGGCCAGTACGGAAAGAATGTGA AAAAATAAGCAGGACACA <u>ATT</u> ACAACATAAAAATATCTAA GCATTGCAAAGGCAGACAATAAAATTATTGACGCTTAA	1125
	TTAAGCGTCAATAATTATTGTCGCCTTGCAAATGCTTAGAT ATATTTTGTAGTTGTAATTGTGTCTGCTTATTCTCACATT CTTCCGTA <u>CTGGCCTGGGAAC</u> CTCCTGTTCTT	1126
	AGGACACA <u>ATT</u> ACAAC	1127
	AGTTGTAATTGTGTCTT	1128

EXAMPLE 9

Cystic Fibrosis - CFTR

Cystic fibrosis is a lethal disease affecting approximately one in 2,500 live Caucasian 10 births and is the most common autosomal recessive disease in Caucasians. Patients with this disease have reduced chloride ion permeability in the secretory and absorptive cells of organs with epithelial cell linings, including the airways, pancreas, intestine, sweat glands and male genital tract. This, in turn, reduces the transport of water across the epithelia. The lungs and the GI tract are the predominant organ systems affected in this disease and the pathology is characterized by blocking of the respiratory and GI 15 tracts with viscous mucus. The chloride impermeability in affected tissues is due to mutations in a specific chloride channel, the cystic fibrosis transmembrane conductance regulator protein (CFTR), which prevents normal passage of chloride ions through the cell membrane (Welsh et al., Neuron, 8:821-829 (1992)). Damage to the lungs due to mucus blockage, frequent bacterial infections and inflammation is the primary cause of morbidity and mortality in CF patients and, although maintenance therapy has 20 improved the quality of patients' lives, the median age at death is still only around 30 years. There is no effective treatment for the disease, and therapeutic research is focused on gene therapy using

exogenous transgenes in viral vectors and/or activating the defective or other chloride channels in the cell membrane to normalize chloride permeability (Tizzano et al., J. Pediat., 120:337-349 (1992)). However, the death of a teenage patient treated with an adenovirus vector carrying an exogenous CFTR gene in clinical trials in the late 1990's has impacted this area of research.

5 The oligonucleotides of the invention for correction of the CFTR gene are attached as a table.

Table 16
CFTR Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Ala46Asp GCT to GAT	AAGGATACAGACAGCGCTGGAATTGTCAGACATATAACAAA TCCCTCTGTTGATTCTG <u>CT</u> GACAATCTATCTGAAAAATTGGA AAGGTATGTTCATGTACATTGTTAGTTGAAGAGAG	1129
	CTCTCTCAACTAAACAATGTACATGAACATACCTTCCAATT TTCAGATAGATTGTC <u>AG</u> CAGAACATCACAGAAGGGATTGGTA TATGTCTGACAATTCCAGGCCTGTCTGTATCCTT	1130
	TGATTCTG <u>CT</u> GACAATC	1131
	GATTGTC <u>AG</u> CAGAACATCA	1132
Cystic fibrosis Ser50Tyr TCT to TAT	AGCGCCTGGAATTGTCAGACATATAACCAATCCCTCTGTTG ATTCTGCTGACAATCTAT <u>CT</u> GAAAAATTGGAAAGGTATGTTCA TGTACATTGTTAGTTGAAGAGAGAAATTCATATTA	1133
	TAATATGAATTCTCTTCAACTAAACAATGTACATGAACATA CCTTCCAATTTC <u>AG</u> ATAGATTGTCAGCAGAACATCACAGAA GGGATTGGTATATGTC <u>CT</u> GACAATTCCAGGCCT	1134
	CAATCTAT <u>CT</u> GAAAAAT	1135
	ATTTTC <u>AG</u> ATAGATTG	1136
	AGGACAACTAAAATTGCACTGCAACTTATTGGTCCCCT TTTATTCTTGCAG <u>AG</u> ATGGGATAGAGAGCTGGCTCAA GAAAAATCCTAAACTCATTAATGCCCTCGGCAT	1137
Congenital absence of vas deferens Glu56Lys GAA-AAA	ATCGCCGAAGGGCATTAAATGAGTTAGGATTTCTTGAAGC CAGCTCTATCCATT <u>CT</u> CTGCAAAAGAATAAAAGTGGGA CCAATAAGTTGCATGTGCAAATATTAGTTGTCCCT	1138
	T <u>TC</u> GCAG <u>AG</u> ATGGGAT	1139
	ATCCCATTCTGCAA	1140

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Trp57Gly TGG to GGG	AGGACAACTAAAATTTGCACATGCAACTATTGGTCCCACT TTTATTCTTTGCAGAGAATGGGATAGAGAGCTGGCTTC AAAAATCTAAACTCATTAATGCCCTCGGCGAT	1141
	ATGCCGAAGGGCATTAATGAGTTAGGATTTCTTG CAGCTCTCTATCCCATTCTGCAAAGAATAAAAGTGG CCAATAAGTTGCATGTGCAAATATTAGTTGTCCT	1142
	TTTGCAGAGAATGGGAT	1143
	ATCCCATTCTGCAA	1144
Cystic fibrosis Trp57Term TGG to TGA	AACTAAAATATTGCACATGCAACTATTGGTCCCACTTTTAT TCTTTGCAGAGAATGGGATAGAGAGCTGGCTCAAAGAAAA ATCCTAAACTCATTAATGCCCTCGGCGATGTTT	1145
	AAAACATGCCGAAGGGCATTAATGAGTTAGGATTTCTT GAAGCCAGCTCTATCCCATTCTGCAAAGAATAAAAGT GGGACCAATAAGTTGCATGTGCAAATATTAGTT	1146
	AGAGAATGGGATAGAGA	1147
	TCTCTATCCCATTCTC	1148
Congenital absence of vas deferens Asp58Asn GAT to AAT	ACTAAAATATTGCACATGCAACTATTGGTCCCACTTTTATT CTTTGCAGAGAATGGGATAGAGAGCTGGCTCAAAGAAAAA TCCTAAACTCATTAATGCCCTCGGCGATGTTT	1149
	AAAACATGCCGAAGGGCATTAATGAGTTAGGATTTCTT TGAAGCCAGCTCTATCCCATTCTGCAAAGAATAAAAG GGGACCAATAAGTTGCATGTGCAAATATTAGT	1150
	GAGAATGGGATAGAGAG	1151
	CTCTCTATCCCATTCTC	1152
Cystic fibrosis Glu60Term GAG to TAG	ATATTGACATGCAACTATTGGTCCCACTTTTATTCTTTG CAGAGAATGGGATAGAGAGCTGGCTCAAAGAAAAATCCTAA ACTCATTAATGCCCTCGGCGATGTTTCTGGA	1153
	TCCAGAAAAACATGCCGAAGGGCATTAATGAGTTAGGAT TTTCTTGAAGCCAGCTCTATCCCATTCTGCAAAGAA AAAAAGTGGACCAATAAGTTGCATGTGCAAATAT	1154
	GGGATAGAGAGCTGGCT	1155
	AGCCAGCTCTATCCC	1156

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:	
Cystic fibrosis Pro67Leu CCT to CTT	GGTCCCACTTTATTCTTTCAGAGAATGGGATAGAGAGC TGGCTCAAAGAAAAT <u>C</u> CTAAACTCATTAATGCCCTCGGC GATGTCTCTGGAGATTATGTTCTATGGAATCTT	1157	
	AAGATTCCATAGAACATAAATCTCCAGAAAAACATGCCGAA GGGCATTAATGAGTT <u>AG</u> GATTTCTTGAAGCCAGCTCT ATCCCATTCTCTGAAAAGAATAAAAGTGGGACC	1158	
	GAAAAAT <u>C</u> CTAAACTCA	1159	
	TGAGTT <u>AGG</u> ATTTC	1160	
Cystic fibrosis Arg74Trp CGG to TGG	TGCAGAGAATGGGATAGAGAGCTGGCTCAAAGAAAATCCT AAACTCATTAATGCCCT <u>C</u> GGCGATGTTCTGGAGATT TGTTCTATGGAATCTTTATATTAGGGTAAGGA	1161	
	TCCTTACCCCTAAATATAAAAGATTCCATAGAACATAAATCT CCAGAAAAACATGCCGAGGGCATTAAATGAGTTAGGATT TTCTTGAAGCCAGCTCTATCCCATTCTGCA	1162	
	ATGCCCT <u>C</u> GGCGATGT	1163	
	ACATGCCGAGGGCAT	1164	
Congenital absence of vas deferens ARG75GLN CGA to CAA	GAGAATGGGATAGAGAGCTGGCTCAAAGAAAATCCTAAAC TCATTAATGCCCTCGGC <u>G</u> ATGTTCTGGAGATTATGTT CTATGGAATCTTTATATTAGGGTAAGGATCTC	1165	
	GAGATCCTACCCCTAAATATAAAAGATTCCATAGAACATAA ATCTCCAGAAAAACAT <u>C</u> GCCGAGGGCATTAAATGAGTTAG GATTTCTTGAAGCCAGCTCTATCCCATTCTC	1166	
	CCTCGGC <u>G</u> ATGTTT	1167	
	AAAAACAT <u>C</u> GCCGAAGG	1168	
Cystic fibrosis Arg75Leu CGA to CTA	GAGAATGGGATAGAGAGCTGGCTCAAAGAAAATCCTAAAC TCATTAATGCCCTCGGC <u>G</u> ATGTTCTGGAGATTATGTT CTATGGAATCTTTATATTAGGGTAAGGATCTC	1169	
	GAGATCCTACCCCTAAATATAAAAGATTCCATAGAACATAA ATCTCCAGAAAAACAT <u>C</u> GCCGAGGGCATTAAATGAGTTAG GATTTCTTGAAGCCAGCTCTATCCCATTCTC	1170	
	CCTCGGC <u>G</u> ATGTTT	1171	
	AAAAACAT <u>C</u> GCCGAAGG	1172	
15	Cystic fibrosis Arg75Term CGA to TGA	AGAGAATGGGATAGAGAGCTGGCTCAAAGAAAATCCTAAAC CTCATTAATGCCCTCGGC <u>G</u> ATGTTCTGGAGATTATGTT TCTATGGAATCTTTATATTAGGGTAAGGATCT	1173

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGATCCTAACCCCTAAATATAAAAAGATTCCATAGAACATAAA TCTCCAGAAAAACATCGCCGAAGGGCATTAATGAGTTAGG ATTTTCTTGAAGCCAGCTCTATCCCATTCTCT	1174
	CCCTTCGG <u>C</u> GATGTTT	1175
	AAAACATCGCCGAAGGG	1176
Cystic fibrosis Gly85Glu GGA to GAA	AAAATCCTAAACTCATTAATGCCCTCGGCGATGTTTTCTG GAGATTATGTTCTAT <u>GG</u> AATCTTTATATTAGGGTAAGG ATCTCATTGTACATTCAATTATGTATCACATAACT	1177
	AGTTATGTGATACATAATGAATGTACAATGAGATCCTTACCC CTAAATATAAAAGATT <u>CC</u> CATAGAACATAAAATCTCCAGAAAAA ACATGCCGAAGGGCATTAATGAGTTAGGATTT	1178
	GTTCTAT <u>GG</u> AATCTTT	1179
	AAAAGATT <u>CC</u> CATAGAAC	1180
Cystic fibrosis Gly85Val GGA to GTA	AAAATCCTAAACTCATTAATGCCCTCGGCGATGTTTTCTG GAGATTATGTTCTAT <u>GG</u> AATCTTTATATTAGGGTAAGG ATCTCATTGTACATTCAATTATGTATCACATAACT	1181
	AGTTATGTGATACATAATGAATGTACAATGAGATCCTTACCC CTAAATATAAAAGATT <u>CC</u> CATAGAACATAAAATCTCCAGAAAAA ACATGCCGAAGGGCATTAATGAGTTAGGATTT	1182
	GTTCTAT <u>GG</u> AATCTTT	1183
	AAAAGATT <u>CC</u> CATAGAAC	1184
Cystic fibrosis Leu88Ser TTA to TCA	AACTCATTAATGCCCTCGGCGATGTTTTCTGGAGATTAT GTTCTAT <u>GG</u> AATCTTTATATTAGGGTAAGGATCTCATT GTACATTCAATTATGTATCACATAACTATATGCATT	1185
	AATGCATATAGTTATGTGATACATAATGAATGTACAATGAGA TCCTTACCCCTAAATATAAAAGATT <u>CC</u> CATAGAACATAAAATCT CCAGAAAAACATGCCGAAGGGCATTAATGAGTT	1186
	AATCTTTATATTAG	1187
	CTAAATATAAAAGATT	1188
Cystic fibrosis Phe87Leu TTT to CTT	CCTAAACTCATTAATGCCCTCGGCGATGTTTTCTGGAGAT TTATGTTCTAT <u>GG</u> AATCTTTATATTAGGGTAAGGATCTC ATTGTACATTCAATTATGTATCACATAACTATATG	1189
	CATATAGTTATGTGATACATAATGAATGTACAATGAGATCCT TACCCCTAAATATAAA <u>AG</u> ATT <u>CC</u> CATAGAACATAAAATCTCCAG AAAAAACATGCCGAAGGGCATTAATGAGTTAGG	1190

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Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ATGGAATCTTTTATAT	1191
	ATATAAAAAGATTCCAT	1192
Cystic fibrosis Leu88Term TTA to TGA	AACTCATTAATGCCCTCGGCATGTTTTCTGGAGATTAT GTTCTATGGAATCTTTTATATTAGGGTAAGGATCTCATT GTACATTCAATTGTATCACATAACTATATGCATT	1193
	AATGCATATAGTTATGTGATACATAATGAATGTACAATGAGA TCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAAATCT CCAGAAAAAAACATGCCGAAGGGCATTAAATGAGTT	1194
	AATCTTTTATATTAG	1195
	CTAAATATAAAAAGATT	1196
Cystic fibrosis Leu88Term TTA to TAA	AACTCATTAATGCCCTCGGCATGTTTTCTGGAGATTAT GTTCTATGGAATCTTTTATATTAGGGTAAGGATCTCATT GTACATTCAATTGTATCACATAACTATATGCATT	1197
	AATGCATATAGTTATGTGATACATAATGAATGTACAATGAGA TCCTTACCCCTAAATATAAAAAGATTCCATAGAACATAAATCT CCAGAAAAAAACATGCCGAAGGGCATTAAATGAGTT	1198
	AATCTTTTATATTAG	1199
	CTAAATATAAAAAGATT	1200
Cystic fibrosis Gly91Arg GGG to AGG	AATGCCCTCGGCATGTTTTCTGGAGATTATGTTCTATG GAATCTTTTATATTAGGGTAAGGATCTCATTGTACATT ATTATGTATCACATAACTATATGCATTGTGAT	1201
	ATCACAAAAATGCATATAGTTATGTGATACATAATGAATGTAC AAATGAGATCCTACCCCTAAATATAAAAAGATTCCATAGAAC ATAAACTCCAGAAAAAAACATGCCGAAGGGCATT	1202
	TATATTAGGGTAAGG	1203
	CCTTACCCCTAAATATA	1204
10 Cystic fibrosis Gln98Arg CAG to CGG	AATAAATGAAATTAAATTCTGTTTCCCCTTGAGGAA GTCACCAAAGCAGTACAGCCTCTTACTGGGAAGAACATA GCTTCCTATGACCCGGATAACAAGGAGGAACGCTC	1205
	GAGCGTTCCCTGTTATCCGGGTAGGAAGCTATGATT CTTCCCAGTAAGAGAGGCTGTACTGCTTGGTACTCCTAC AAAAGGGAAAAACAGAGAAATTAAATTTCATT	1206
	AGCAGTACAGCCTCTCT	1207
	AGAGAGGCTGTACTGCT	1208

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Gln98Term CAG-TAG	AAATAATGAAATTAA <u>TTCTCTGT</u> TTTCCCGCTTGAGGA AGTCACCAAAGCAGTACAGCCTCTCTACTGGGAAGAACAT AGCTCCTATGACCCGGATAACAAGGAGGAACGCT	1209
	AGCGTTCTCCTGTTATCCGGGT <u>CATAGGAAGCTATGATT</u> TTC <u>CCAGTAAGAGAGGCTG</u> TACTGCTTGGTGACTTCCTACA AAAGGGAAAAACAGAGAAATTAAATTCA <u>TTT</u>	1210
	AAGCAGTAC <u>AGCCTCTC</u>	1211
	GAGAGGCT <u>G</u> TACTGCTT	1212
Cystic fibrosis Ser108Phe TCC to TTC	CCCTTTGAGTCACCAAAGCAGTACAGCCTCTTAC TGGGAAGAACATAGCTT <u>CCTATGACCCGGATAACAAGGAGG</u> AACGCTCTATCGCGATTATCTAGGCATAGGCTTATG	1213
	CATAAGCCTATGCCTAGATAAA <u>ATCGCGATAGAGCGTTCTCC</u> TTGTTATCCGGGT <u>CATAGGAAGCTATGATTCTCCCAGTAAG</u> AGAGGCTGTA <u>T</u> ACTGCTTGGTGACTTCCTACAAAAGGG	1214
	CATAGCTT <u>CCTATGACC</u>	1215
	GGTCAT <u>AGGAAGCTATG</u>	1216
Cystic fibrosis Tyr109Cys TAT to TGT	TTTGAGTCACCAAAGCAGTACAGCCTCTTACTGG GAAGAACATAGCTT <u>CCTATGACCCGGATAACAAGGAGGAAC</u> GCTCTATCGCGATTATCTAGGCATAGGCTTATGCCT	1217
	AGGCATAAGCCTATGCCTAGATAAA <u>ATCGCGATAGAGCGTTCC</u> TCCTGTTATCCGGGT <u>CATAGGAAGCTATGATTCTCCCAGT</u> AAGAGAGGCTGTA <u>T</u> ACTGCTTGGTGACTTCCTACAAA	1218
	AGCTT <u>CCTATGACCCGG</u>	1219
	CCGGGT <u>CATAGGAAGCT</u>	1220
Cystic fibrosis Asp110His GAC to CAC	TTGAGTCACCAAAGCAGTACAGCCTCTTACTGGGA AGAACATAGCTT <u>CCTATGACCCGGATAACAAGGAGGAACGC</u> TCTATCGCGATTATCTAGGCATAGGCTTATGCCTC	1221
	GAAGGCATAAGCCTATGCCTAGATAAA <u>ATCGCGATAGAGCGTT</u> CCTCCTGTTATCCGGGT <u>CATAGGAAGCTATGATTCTCCCAGT</u> GTAAGAGAGGCTGTA <u>T</u> ACTGCTTGGTGACTTCCTACAA	1222
	CTT <u>CCTATGACCCGGAT</u>	1223
	ATCCGGGT <u>CATAGGAAG</u>	1224

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Congenital absence of vas deferens Pro111Leu CCG to CTG	AGGAAGTCACCAAAGCAGTACAGCCTCTTACTGGGAAGAA TCATAGCTTCCTATGACCGGATAACAAGGAGGAACGCTCA TCGCGATTATCTAGGCATAGGCTTATGCCTCTT	1225
	AAGAGAAGGCATAAGCCTATGCCTAGATAAACGCGATAGAG CGTCCCTCTTGTATCC <u>GGGT</u> CATAGGAAGCTATGATTCTT CCCAGTAAGAGAGGGCTGTACTGCTTGTTGACTTCCT	1226
	CTATGACC <u>CCGG</u> ATAACA	1227
	TGTTATCC <u>GGGT</u> CATAG	1228
5 Cystic fibrosis Arg117Cys CGC to TGC	GTACAGCCTCTTACTGGGAAGAACATAGCTTCCTATGAC CCGGATAACAAGGAGGAAC <u>G</u> CTCTATCGCGATTATCTAGGC ATAGGCTTATGCCTCTTATTGTGAGGACACTGC	1229
	GCAGTGTCTCACAATAAGAGAAGGCATAAGCCTATGCC GATAAAATCGCGATAGAG <u>G</u> TTCCCTCTTGTATCCGGGTCA AGGAAGCTATGATTCTCCCAGTAAGAGAGGGCTGTAC	1230
	AGGAGGAAC <u>G</u> CTCTATC	1231
	GATAGAG <u>G</u> TTCCCTCCT	1232
	TACAGCCTCTTACTGGGAAGAACATAGCTTCCTATGACC CGGATAACAAGGAGGAAC <u>G</u> CTCTATCGCGATTATCTAGGC TAGGCTTATGCCTCTTATTGTGAGGACACTGCT	1233
10 Cystic fibrosis Arg117His CGC to CAC	AGCAGTGTCTCACAATAAGAGAAGGCATAAGCCTATGCC AGATAAAATCGCGATAGAG <u>G</u> TTCCCTCTTGTATCCGGGTCA TAGGAAGCTATGATTCTCCCAGTAAGAGAGGGCTGTAC	1234
	GGAGGAAC <u>G</u> CTCTATCG	1235
	CGATAGAG <u>G</u> TTCCCTCC	1236
	TACAGCCTCTTACTGGGAAGAACATAGCTTCCTATGACC CGGATAACAAGGAGGAAC <u>G</u> CTCTATCGCGATTATCTAGGC TAGGCTTATGCCTCTTATTGTGAGGACACTGCT	1237
	AGCAGTGTCTCACAATAAGAGAAGGCATAAGCCTATGCC AGATAAAATCGCGATAGAG <u>G</u> TTCCCTCTTGTATCCGGGTCA TAGGAAGCTATGATTCTCCCAGTAAGAGAGGGCTGTAC	1238
Cystic fibrosis Arg117Leu CGC to CTC	GGAGGAAC <u>G</u> CTCTATCG	1239
	CGATAGAG <u>G</u> TTCCCTCC	1240

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Arg117Pro CGC to CCC	TACAGCCTCTTACTGGGAAGAACATAGCTTCCTATGACC CGGATAACAAGGAGGAAC <u>G</u> CTCTATCGCGATTATCTAGGCA TAGGCTTATGCCTCTTTATTGTGAGGACACTGCT	1241
	AGCAGTGTCTCACAAATAAGAGAAGGCATAAGCCTATGCCT AGATAATCGCGATAGAG <u>G</u> TTCTCCCTGTTATCCGGGTCA TAGGAAGCTATGATTCTCCCAGTAAGAGAGGGCTGTA	1242
	GGAGGAAC <u>G</u> CTCTATCG	1243
	CGATAGAG <u>G</u> TTCCCTCC	1244
Cystic fibrosis Ala120Thr GCG-ACG	CTCTTACTGGGAAGAACATAGCTTCCTATGACCCGGATAAC AAGGAGGAAC <u>G</u> CTCTAT <u>G</u> CGATTATCTAGGCATAGGCTTA TGCCCTCTTTATTGTGAGGACACTGCTCCTACACC	1245
	GGTGTAGGAGCAGTGTCTCACAAATAAGAGAAGGCATAAG CCTATGCCTAGATAATCGCGATAGAG <u>G</u> TTCTCCCTGTTA TCCGGGTCAAGGAAGCTATGATTCTCCCAGTAAGAG	1246
	GCTCTAT <u>G</u> CGATTAT	1247
	ATAAA <u>T</u> CGCGATAGAGC	1248
Cystic fibrosis Tyr122Term TAT to TAA	GGGAAGAACATAGCTTCCTATGACCCGGATAACAAGGAGGA ACGCTCTATCGCGATTAT <u>T</u> CTAGGCATAGGCTTATGCCTCT CTTTATTGTGAGGACACTGCTCCTACACCCAGCCATT	1249
	AATGGCTGGGTAGGAGCAGTGTCTCACAAATAAGAGAA GGCATAAGCCTATGCCTAG <u>A</u> AAATCGCGATAGAG <u>G</u> TTCT CCTTGTATCCGGGTCAAGGAAGCTATGATTCTCCC	1250
	GCGATTAT <u>T</u> CTAGGCAT	1251
	ATGCCTAG <u>A</u> AAATCGC	1252
Cystic fibrosis Gly126Asp GGC-GAC	TAGCTTCCTATGACCCGGATAACAAGGAGGAAC <u>G</u> CTCTATCG CGATTATCTAGGCATAG <u>G</u> CTTATGCCTCTTTATTGTGAG GACACTGCTCCTACACCCAGCCATTGGCCTCA	1253
	TGAAGGCCAAAATGGCTGGGTAGGAGCAGTGTCTCAC AATAAAAGAGAAGGCATAAG <u>C</u> CTATGCCTAGATAAA <u>T</u> CGCGAT AGAG <u>G</u> TTCTCCTGTTATCCGGGTCAAGGAAGCTA	1254
	AGGCATAG <u>G</u> CTTATGCC	1255
	GGCATAAG <u>C</u> CTATGCCT	1256

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis His139Arg CAC to CGC	TCGCATTTAGGCATAGGCTTATGCCCTCTTTATTGT GAGGACACTGCTCCTAC <u>ACCCAGCC</u> ATTTGGCCTTCATCA CATTGGAATGCAGATGAGAATAGCTATGTTAGTT	1257
	AAACTAACATAGCTATTCTCATCTGCATTCCAATGTGATGAA GGCCAAAAATGGCTGGGT <u>G</u> TAGGAGCAGTGTCCCTACAATA AAGAGAAGGCATAAGCCTATGCCTAGATAAAATCGCGA	1258
	GCTCCTAC <u>ACCCAGCC</u> A	1259
	TGGCTGGGT <u>G</u> TAGGAGC	1260
Cystic fibrosis Ala141Asp GCC to GAC	TTTATCTAGGCATAGGCTTATGCCCTCTTTATTGTGAGGAC ACTGCTCCTACACCCAG <u>CC</u> ATTTGGCCTTCATCACATTG AATGCAGATGAGAATAGCTATGTTAGTTGATT	1261
	TAAATCAAACAAACATAGCTATTCTCATCTGCATTCCAATGT GATGAAGGCCAAAATGGCTGGGTGTAGGAGCAGTGTCCCTC ACAATAAAGAGAAGGCATAAGCCTATGCCTAGATAAA	1262
	ACACCCAG <u>CC</u> ATTTTG	1263
	CAAAAATGGCTGGGTGT	1264
Cystic fibrosis Ile148Thr ATT to ACT	GCCTCTCTTTATTGTGAGGACACTGCTCCTACACCCAGCC TTTTGGCCTTCATCACAT <u>GG</u> ATGCAGATGAGAATAGCTAT GTTTAGTTGATTATAAGAAGGTAATACTTCCTTG	1265
	CAAGGAAGTATTACCTCTTATAAAATCAAACAAACATAGCTA TTCTCATCTGCATTCCA <u>AT</u> GTGATGAAGGCCAAAATGGCTG GGTGTAGGAGCAGTGTCCCTACAATAAAGAGAAGGC	1266
	TCATCACAT <u>GG</u> ATGC	1267
	GCATTCCA <u>AT</u> GTGATGA	1268
Cystic fibrosis Gly149Arg GGA to AGA	CTTCTCTTTATTGTGAGGACACTGCTCCTACACCCAGCCATT TTGGCCTTCATCACAT <u>GG</u> ATGCAGATGAGAATAGCTATGTT TAGTTGATTATAAGAAGGTAATACTTCCTTGCA	1269
	TGCAAGGAAGTATTACCTCTTATAAAATCAAACAAACATAGC TATTCTCATCTGCATTCCA <u>AT</u> GTGATGAAGGCCAAAATGGCT GGGTGTAGGAGCAGTGTCCCTACAATAAAGAGAAG	1270
	ATCACATT <u>GG</u> ATGCAG	1271
	CTGCATTCCA <u>AT</u> GTGAT	1272

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Cystic fibrosis Gln151Term CAG to TAG	TTTATTGTGAGGACACTGCTCCTACACCCAGCCATTTGGC CTTCATCACATTGGAAT <u>G</u> CAGATGAGAATAGCTATGTTAGTT TGATTTATAAGAAGGTAATACTCCTTGACAGGCC	1273
	GGCCTGTGCAAGGAAGTATTACCTCTTATAAATCAAACAAA CATAGCTATTCTCATCT <u>G</u> CATTCCAATGTGATGAAGGCCAAA ATGGCTGGGTGTAGGAGCAGTGTCCCTACAATAAA	1274
	TTGGAAT <u>G</u> CAGATGAGA	1275
	TCTCATCT <u>G</u> CATTCCA	1276
Cystic fibrosis Lys166Glu AAG-GAG	AATATATTTGTATTTGTTGAAATTATCTAACCTTCCATT TTCTTTAGACTTT <u>A</u> AGCTGTCAAGCCGTGTTAGATAAAA TAAGTATTGGACAACTTGTTAGTCTCCTTCCA	1277
	TGGAAAGGAGACTAACAGTTCCAACACTTATTTATCTAG AACACGGCTTGACAGCT <u>T</u> AAAGTCTAAAAGAAAAATGGAAA GTTAGATAATTCAACAAACAAAACAAATATATT	1278
	AGACTTT <u>A</u> AGCTGTCA	1279
	TGACAGCT <u>T</u> AAAGTCT	1280
Cystic fibrosis Ile175Val ATA-GTA	TTATCTAACCTTCCATTTCCTTTAGACTTTAAAGCTGTCAAG CCGTGTTCTAGATAAAA <u>A</u> AGTATTGGACAACCTGTTAGTCTC CTTCCAACAAACCTGAACAAATTGATGAAGTAT	1281
	ATACTTCATCAAATTGTTAGGTTGTTGGAAAGGAGACTAAC AAGTTGTCCAACACTT <u>A</u> TTTATCTAGAACACGGCTTGACAGC TTAAAGTCTAAAAGAAAAATGGAAAGTTAGATAAA	1282
	TAGATAAAA <u>A</u> AGTATT	1283
	AATACTT <u>A</u> TTTATCTA	1284
Cystic fibrosis Gly178Arg GGA to AGA	TTCCATTTCCTTTAGACTTTAAAGCTGTCAAGCCGTGTTCT AGATAAAATAAGTATT <u>G</u> GACAACCTGTTAGTCTCCTTCCAAC AACCTGAACAAATTGATGAAGTATGTACCTATT	1285
	AATAGGTACATACTTCATCAAATTGTTAGGTTGTTGGAAAG GAGACTAACAGTTGTCCAACACTTATTTATCTAGAACACGG CTTGACAGCTTAAAGTCTAAAAGAAAAATGGAAA	1286
	TAAGTATT <u>G</u> GACAACCTT	1287
	AAGTTGTCCAACACTTAA	1288
15 Cystic fibrosis His199Gln CAT to CAG	AAGATACAATGACACCTGTTTGCTGTGCTTTATTTCCAG GGACTTGCAATTGGCACATTCGTGTGGATCGCTCCTTGCAA GTGGCACTCCTCATGGGGCTAATCTGGGAGTTGTTA	1289

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TAACAACTCCCAGATTAGCCCCATGAGGGAGTGCCACTTGC AGGAGCGATCCACACGAA <u>A</u> TGTGCCAATGCAAGTCCCTGGA AAATAAAAGCACAGCAAAA <u>A</u> CAGGTGTCAATTGTATCTT	1290
	TTGGCAC <u>A</u> TTCGTGTG	1291
	CACACGAA <u>A</u> GTGCCAA	1292
Cystic fibrosis His199Tyr CAT to TAT	GGAAGATACAATGACACCTGTTTGCTGTGCTTTATTTCC AGGGACTTGCATTGGC <u>A</u> TTTCGTGTGGATCGCTCCTTGC AA <u>G</u> GTGGCACTCCTCATGGGCTAATCTGGAGTTGT	1293
	ACA <u>A</u> CTCCCAGATTAGCCCCATGAGGGAGTGCCACTTGCAAAG GAGCGATCCACACGAA <u>A</u> GTGCCAATGCAAGTCCCTGGAAA ATAAAAGCACAGCAAAA <u>A</u> CAGGTGTCAATTGTATCTTCC	1294
	CATTGGC <u>A</u> CA <u>A</u> TTCGTGTG	1295
	CACGAA <u>A</u> GTGCCAATG	1296
Cystic fibrosis Pro205Ser CCT to TCT	TGTTTTGCTGTGCTTTATTTCCAGGGACTTGCA <u>T</u> GGCAC ATT <u>C</u> GTGTGGATCGCT <u>C</u> TTTGCAAGTGGCA <u>T</u> CCCTCATGG GGCTAATCTGGAGTTGTACAGGC <u>G</u> T <u>C</u> GC <u>T</u> GC <u>C</u> TTCT	1297
	AGAAGGCAGACGCCTGTA <u>A</u> CAACTCCCAGATTAGCCCCATG AGGAGTGCCACTTGCAAA <u>GG</u> AGCGATCCACACGAA <u>A</u> GTGC CAATGCAAGTCCCTGGAAA <u>A</u> AAAGCACAGCAAAAACA	1298
	GGATCG <u>C</u> CT <u>C</u> TTGCAA	1299
	TTGCAA <u>AGG</u> AGCGATCC	1300
Cystic fibrosis Leu206Trp TTG to TGG	TTGCTGTGCTTTATTTCCAGGGACTTGCA <u>T</u> GGCAC <u>A</u> TT CGTGTGGATCGCT <u>C</u> TTTG <u>C</u> AA <u>G</u> GTGGCA <u>T</u> CCCTCATGGGC TAATCTGGAGTTGTACAGGC <u>G</u> T <u>C</u> GC <u>T</u> GC <u>C</u> TTCTGTGG	1301
	CCACAGAAGGCAGACGCCTGTA <u>A</u> CAACTCCCAGATTAGCCC CATGAGGAGTGCCACTTG <u>C</u> AA <u>AGG</u> AGCGATCCACACGAA <u>A</u> GTGCCAATGCAAGTCCCTGGAAA <u>A</u> AAAGCACAGCAAA	1302
	CGCT <u>C</u> TTTG <u>C</u> AA <u>G</u> GTGG	1303
	CCACTTG <u>C</u> AA <u>AGG</u> AGCG	1304
	TTCGTGTGGATCGCT <u>C</u> TTTG <u>C</u> AA <u>G</u> GTGGCA <u>T</u> CCCTCATGGG GCTAATCTGGAGTTGTACAGGC <u>G</u> T <u>C</u> GC <u>T</u> GC <u>C</u> TTCTGTGGACT TGGTT <u>C</u> CTGATAGTCC <u>T</u> GC <u>C</u> CTTGC <u>C</u> CTTTCAGGC <u>G</u> GGC	1305
Cystic fibrosis Gln220Term CAG to TAG	GCCCAGCCTGAAAA <u>AGG</u> CAAGGACTATCAGGAA <u>ACC</u> AGT CCACAGAAGGCAGACGCCTGTA <u>A</u> CAACTCCCAGATTAGCCC CATGAGGAGTGCCACTTG <u>C</u> AA <u>AGG</u> AGCGATCCACACGAA	1306

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	AGTTGTTACAGGCGTCT	1307
	AGACGCCTGTAACAAC	1308
Cystic fibrosis Cys225Arg TGT-CGT	CCTTGCAAGTGGCACTCCTCATGGGGCTAATCTGGGAGTT GTTACAGGCGTCTGCCCTCTGTGGACTGGTTCTGATAGT CCTTGCCCTTTTCAGGCTGGCTAGGGAGAATGATGA	1309
	TCATCATTCTCCCTAGCCCAGCCTGAAAAAGGGCAAGGACTA TCAGGAAACCAAGTCCACAGAAGGCAGACGCCTGTAACAAC TCCCAGATTAGCCCCATGAGGAGTGCCACTTGCAAAGG	1310
	CTGCCTTCGTGGACTT	1311
	AAGTCCACAGAAGGCAG	1312
Cystic fibrosis Val232Asp GTC to GAC	TGGGGCTAATCTGGGAGTTGTTACAGGCGTCTGCCCTCTGT GGACTTGGTTCTGATAGTCCTGCCCTTTTCAGGCTGGG CTAGGGAGAATGATGATGAAGTACAGGTAGCAACCTAT	1313
	ATAGGTTGCTACCTGTACTTCATCATCATTCTCCCTAGCCCA GCCTGAAAAAGGGCAAGGACTATCAGGAAACCAAGTCCACA GAAGGCAGACGCCTGTAACAACCTCCAGATTAGCCCCA	1314
	CCTGATAGTCCTGCC	1315
	GGGCAAGGACTATCAGG	1316
Cystic fibrosis Gly239Arg GGG to AGG	GTTACAGGCGTCTGCCCTCTGTGGACTTGGTTCTGATAGT CCTTGCCCTTTTCAGGCTGGCTAGGGAGAATGATGATGAA GTACAGGTAGCAACCTATTCATAACTTGAAAGTTT	1317
	AAACTTTCAAGTTATGAAAATAGGTTGCTACCTGTACTTCATC ATCATTCTCCCTAGCCCAGCCTGAAAAAGGGCAAGGACTATC AGGAAACCAAGTCCACAGAAGGCAGACGCCTGTAAC	1318
	TTTCAGGCTGGCTAGG	1319
	CCTAGCCCAGCCTGAAA	1320

EXAMPLE 10
Cyclin-dependent kinase inhibitor 2A - CDKN2A

The human CDKN2A gene was also designated MTS-1 for multiple tumor suppressor-1 and has been implicated in multiple cancers including, for example, malignant melanoma. Malignant melanoma is a cutaneous neoplasm of melanocytes. Melanomas generally have features of asymmetry, irregular border, variegated color, and diameter greater than 6 mm. The precise cause of melanoma is

unknown, but sunlight and heredity are risk factors. Melanoma has been increasing during the past few decades.

The CDKN2A gene has been found to be homozygously deleted at high frequency in cell lines derived from tumors of lung, breast, brain, bone, skin, bladder, kidney, ovary, and lymphocyte.

Melanoma cell lines carried at least one copy of CDKN2A in combination with a deleted allele. Melanoma cell lines that carried at least 1 copy of CDKN2A frequently showed nonsense, missense, or frameshift mutations in the gene. Thus, CDKN2A may rival p53 (see Example 5) in the universality of its involvement in tumorigenesis. The attached table discloses the correcting oligonucleotide base sequences for the CDKN2A oligonucleotides of the invention.

Table 17
CDKN2A Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Melanoma Trp15Term TGG-TAG	GGGCGGGGGGAGCAGCATGGAGCCGGCGGGAGCAC CATGGAGCCTTCGGCTGACT <u>G</u> GCTGGCCACGGCCGCCCC GGGGTCGGGTAGAGGAGGTGCAGGGCGCTGCTGGAGGCGGG	1321
	CCCGCCTCCAGCAGCGCCCGCACCTCCTCTACCCGACCCCG GGCCCGGCCGTGCCAG <u>C</u> AGTCAGCCGAAGGCTCCATGC TGCTCCCCGCCGCCGGCTCCATGCTGCTCCCCGCCGCC	1322
	GGCTGACT <u>G</u> GCTGGCCA	1323
	TGGCCAG <u>C</u> AGTCAGCC	1324
Melanoma Leu16Pro CTG-CCG	CGGCGGGGAGCAGCATGGAGCCGGCGGGAGCAC GGAGCCTTCGGCTGACTGG <u>C</u> GGCCACGGCCGCGGCCGG GGTCGGGTAGAGGAGGTGCAGGGCGCTGCTGGAGGCGGGGG C	1325
	GCCCCCGCCTCCAGCAGCGCCCGCACCTCCTCTACCCGACC CCGGGCCGCCGGCC <u>A</u> GCCAGTCAGCCGAAGGCTCC ATGCTGCTCCCCGCCGCCGGCTCCATGCTGCTCCCCGCCG	1326
	TGACTGG <u>C</u> GGCCACGG	1327
	CCGTGGCC <u>A</u> GCCAGTC	1328
	CGGCGGGGGGAGCAGCATGGAGCCCTCGGCTGACTGGCTG GCCACGGCCGCCGGGG <u>T</u> CGGGTAGAGGAGGTGCAGGG CGCTGCTGGAGGCGGGGGCGCTGCCAACGCACCGAATAG	1329
20 Melanoma Gly23Asp GGT-GAT	CTATTGGTGCCTGGGAGCGCCCCCGCCTCCAGCAGCGC CCGCACCTCCTCTACCCGAC <u>CCC</u> GGCCGCC <u>G</u> GGCCA GCCAGTCAGCCGAAGGCTCCATGCTGCTCCCCGCCGCC	1330
	GGCCCCGGGG <u>T</u> CGGGTAG	1331

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CTACCCGACCCCAGGGCC	1332
Melanoma Arg24Pro CGG-CCG	CGGCAGGGAGCAGCATGGAGCCTCGGCTGACTGGCTGGCC ACGGCCGCGGCCGGGGTC <u>GGGTAGAGGAGGTGCGGGCGC</u> TGCTGGAGGCAGGGCGCTGCCAACGCACCGAATAGTTA	1333
	TAACTATTGGTGCCTGGCAGCGCCCCGCCCTCCAGCAGC GCCCGCACCTCCTACCCGACCCCGGGCCGCGCCGTGGC CAGCCAGTCAGCCGAAGGCTCCATGCTGCTCCCCGCCG	1334
	CCGGGGTC <u>GGGTAGAGG</u>	1335
	CCTCTACCCGACCCCGG	1336
Melanoma Leu32Pro CTG-CCG	CGGCTGACTGGCTGGCCACGGCCGCGCCGGGGTCGGGT AGAGGAGGTGCGGGCGCTG <u>TGGAGGCGGGGGCGCTGCC</u> AACGCACCGAATAGTTACGGTCGGAGGCCGATCCAGGTGGG	1337
	CCCACCTGGATCGGCCTCCGACCGTAACATTGGTGCCTG GGCAGCGCCCCCGCCTCC <u>AGCAGCGCCCGCACCTCCTAC</u> CCGACCCCGGGCCGCGGGCGTGGCCAGCCAGTCAGCCG	1338
	GGCGCTG <u>TGGAGGCGG</u>	1339
	CCGCCTCC <u>AGCAGCGCC</u>	1340
	GGCTGGCCACGGCCGCGGCCGGGGTCGGTAGAGGAGGT GCGGGCGCTG <u>GGAGGCGGGGGCGCTGCCAACGCACCG</u> AA TAGTTACGGTCGGAGGCCGATCCAGGTGGTAGAGGTC	1341
Melanoma Gly35Ala GGG-GCG	GACCTCTACCCACCTGGATCGGCCTCCGACCGTAACATT GGTGCCTGGG <u>CAGCGCCCCCGCCTCCAGCAGCGCCCGAC</u> CTCCTCTACCCGACCCGGGCCGCGGCCGTGGCCAGCC	1342
	GGAGGCGGGGGCGCTGC	1343
	GCAGCGCCCCCGCCTCC	1344
	GGTAGAGGAGGTGCGGGCGCTGCTGGAGGCGGGCGCTG CCCAACGCACCGAATAGTTACGGTCGGAGGCCGATCCAGGTG GGTAGAGGGTCTGCAGCGGGAGCAGGGATGGCGGGCGA	1345
Melanoma Tyr44Terminant TACg-TAA	TCGCCCCCATCCCCTGCTCCCGCTGCAGACCCCTCTACCCAC CTGGATCGGCCTCCGACCGTAACATTGGTGCCTGGCAG CGCCCCCGCCTCCAGCAGCGCCCGCACCTCCTCTACC	1346
	AATAGTTACGGTCGGAG	1347
	CTCCGACCGTAACATT	1348
	TCTCCCATACCTGCCCAACCTGGCTCTGACCACTTGCTC TCTCTGGCAGGT <u>CATGATGATGGGCAGCGCCCGTGGCGG</u> AGCTGCTGCTGCTCCACGGCGCGAGGCCAACTGCGCA	1349
Melanoma Met53Ile ATGa-ATC	TGCGCAGTGGCTCCGGCCGTGGAGCAGCAGCAGCTCCG CCACGCGGGCGCTGCCCAT <u>CATCATGACCTGCCAGAGAGAG</u> CAGAGTGGTCAGAGCCAGGGTGGGGCAGGTATGGGAGA	1350
	GTCATGAT <u>GATGGGCAG</u>	1351

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CTGCCCATCATCATGAC	1352
Melanoma Met54Ile ATGg-ATT	CCCATACTGCCCTACCCCTGGCTCTGACCCTCTGCTCTCT CTGGCAGGTATGATGAT <u>GGGCAGCGCCGCGTGGCGGAGC</u> TGCTGCTGCTCCACGGCGCGAGCCAACTGCGCAGAC	1353
	GTCTGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCAGCAGCT CCGCCACGCGGGCGCTGCCATCATCATGACCTGCCAGAGA GAGCAGAGTGGTCAGAGCCAGGGTGGGGCAGGTATGGG	1354
	ATGATGAT <u>GGGCAGCGC</u>	1355
	GCGCTGCCCATCATCAT	1356
Melanoma Ser56Ile AGC-ATC	GCCGGCCCCCACCCCTGGCTCTGACCATTCTGTTCTCTGGC AGGTATGATGATGGGCAGCGCCGAGTGGCGGAGCTGCTG CTGCTCCACGGCGCGAGCCAACTGCGCCGACCCCGC	1357
	GCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTGGAGCAGCA GCAGCTCCGCCACTCGGGCG <u>CTGCCATCATGACCTGCC</u> AGAGAGAACAGAACATGGTCAGAGCCAGGGTGGGGCCGGC	1358
	GATGGGCAG <u>CGCCCGAG</u>	1359
	CTCGGGCGCTGCCATC	1360
	GGCCCCCACCCCTGGCTCTGACCATTCTGTTCTCTGGCAGG TCATGATGATGGGCAGCGCCGAGTGGCGGAGCTGCTGCTG CTCCACGGCGCGAGCCAACTGCGCCGACCCCGCCAC	1361
Melanoma Ala57Val GCC-GTC	GTGGCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTGGAGCA GCAGCAGCTCCGCCACTCGGGCG <u>CTGCCATCATGACCT</u> GCCAGAGAGAACAGAACATGGTCAGAGCCAGGGTGGGGCC	1362
	GGGCAGCG <u>CCCGAGTGG</u>	1363
	CCACTCGGGCGCTGCC	1364
	CCCCCACCCCTGGCTCTGACCATTCTGTTCTCTGGCAGGT ATGATGATGGGCAGCGCC <u>CGAGTGGCGGAGCTGCTGCTG</u> CCACGGCGCGAGCCAACTGCGCCGACCCCGCCACTC	1365
	GAGTGGCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTGGAG CAGCAGCAGCTCCGCCACTCGGGCG <u>CTGCCATCATGAC</u> CTGCCAGAGAGAACAGAACATGGTCAGAGCCAGGGTGGGGG	1366
Melanoma Arg58Term cCGA-TGA	GCAGCGCC <u>CGAGTGGCG</u>	1367
	CGCCACTCGGGCGCTGC	1368
	CACCCCTGGCTCTGACCATTCTGTTCTCTGGCAGGTATGAT GATGGGCAGCGCCGAGTGGCGGAGCTGCTGCTGCCACG GCGCGGAGCCAACTGCGCCGACCCCGCCACTCTCAC	1369
	GTGAGAGTGGCGGGGTCGGCGCAGTTGGGCTCCGCGCCGTG GAGCAGCAGCAGCTCCGCC <u>ACTCGGGCGCTGCCATCATCA</u> TGACCTGCCAGAGAGAACAGAACATGGTCAGAGCCAGGGTG	1370
	CGCCCGAGTGGCGGAGC	1371

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	GCTCCGCC <u>A</u> CTCGGGCG	1372
Melanoma Leu62Pro CTG-CCG	TCTGACCAC <u>T</u> CTGCTCTCTGGCAGGTATGATGATGGCA GCGCCCGCGTGGCGGAG <u>C</u> TGCTGCTGCTCCACGGCGCGGA GCCCAACTGCGCAGACCC <u>T</u> GCCACTCTCACCCGACCGGT	1373
	ACCGGTCGGGTGAGAGTGGCAGGGTCTGCGCAGTTGGCTC CGCGCCGTGGAGCAGCAG <u>C</u> ACTCCGCCACGCGGGCGCTG CCCATCATCATGACCTGCCAGAGAGAGCAGAGTGGTCAGA	1374
	GGCGGAG <u>C</u> TGCTGCTGC	1375
	GCAGCAG <u>C</u> AGCTCCGCC	1376
5 Melanoma Ala68Val GCG-GTG	TCTGGCAGGTATGATGATGGCAGCGCCCGCGTGGCGGAG CTGCTGCTGCTCCACGGCGGGAG <u>CC</u> AACTGCGCAGACCC TGCCACTCTCACCCGACCGGTGCATGATGCTGCCCGGA	1377
	TCCCGGGCAGCATCATGCACCGGTGGGTGAGAGTGGCAGG GTCTGCGCAGTTGGGCTCC <u>CG</u> CGCCGTGGAGCAGCAGCAGCT CCGCCACGCGGGCGCTGCCCATCATGACCTGCCAGA	1378
	CCACGGCG <u>CG</u> GGAG <u>CC</u> CA	1379
	TGGGCTCC <u>CG</u> CGCCGTGG	1380
	CATGATGATGGG <u>C</u> AGCGCCCGAGTGGCGGAGCTGCTGCTGC TCCACGGCGCGGAG <u>CC</u> AA <u>T</u> CGCGCCACCCGCCACTCTC ACCCGACCCGTGCACGACGCTGCCGGGAGGGCTTCCTG	1381
10 Melanoma Asn71Lys AACt-AAA	CAGGAAGCCCTCCCGGGCAGCGTCGTGCACGGGTGGGTGA GAGTGGCGGGGT <u>CG</u> CGCAG <u>T</u> GGGCTCC <u>CG</u> CGCCGTGGAG CAGCAGCAGCTCCGCCACTCGGGCGCTGCCATCATCATG	1382
	GAG <u>CC</u> AA <u>T</u> CGCGCCGA	1383
	TCGGCGCAG <u>T</u> GGGCTC	1384
	TCATGATGATGGG <u>C</u> AGCGCCCGAGTGGCGGAGCTGCTGCTG CTCCACGGCGCGGAG <u>CC</u> AA <u>T</u> CGCGCCACCCGCCACTCT CACCCGACCCGTGCACGACGCTGCCGGGAGGGCTTCCT	1385
	AGGAAGCCCTCCCGGGCAGCGTCGTGCACGGGTGGGTGAG AGTGGCGGGGT <u>CG</u> CGCAG <u>T</u> GGGCTCC <u>CG</u> CGCCGTGGAGCA GCAGCAGCTCCGCCACTCGGGCGCTGCCATCATCATGA	1386
15 Melanoma Pro81Leu CCC-CTC	GGAG <u>CC</u> AA <u>T</u> CGCGCCG	1387
	CGGCGCAG <u>T</u> GGGCTCC	1388
	AGCTGCTGCTGCTCCACGGCGCGGAG <u>CC</u> AA <u>T</u> CGCGCCGAC CCCGCCACTCTCACCCGAC <u>CC</u> CGTGCACGACGCTGCCGGGA GGGCTTCC <u>CG</u> ACACGCTGGTGGTGC <u>T</u> GCACCCGGGCGG	1389
	CCGGCCCCGGTGCAGCACCACCAGCGTGTCCAGGAAGCCCTC CC <u>CG</u> CAGCGTGTGCACGG <u>T</u> GGTGGAGAGTGGCGGG TCGGCGCAG <u>T</u> GGGCTCC <u>CG</u> CGCCGTGGAGCAGCAGCAGCT	1390
	CACCCGAC <u>CC</u> GTGCACG	1391

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CGTGCACGGTGGGTG	1392
Melanoma Asp84Tyr CGAC-TAC	CTGCTCCACGGCGCGAGGCCAACTGCGCCGACCCCGCCAC TCTCACCCGACCCGTGCAC <u>G</u> ACGCTGCCCGGGAGGGCTTCC TGGACACGCTGGTGGTGCACCGGGCCGGGCGCGGC	1393
	GCCGCGCCCCGGCCCGGTGCAGCACCACCAGCGTGTCCAGG AAGCCCTCCGGGCAGCGT <u>C</u> GTGCACGGTCGGTGAGAGT GGCGGGGTCGGCGCAGTTGGCTCCGCGCCGTGGAGCAG	1394
	CCGTGCAC <u>G</u> ACGCTGCC	1395
	GGCAGCGTCGTGCACGG	1396
5 Melanoma Ala85Thr CGCT-ACT	CTCCACGGCGCGAGGCCAACTGCGCCGACCCCGCCACTCT CACCCGACCCGTGCACGAC <u>G</u> CTGCCCGGGAGGGCTTCC ACACGCTGGTGGTGCACCGGGCCGGGCGCGGCTGG	1397
	CCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAGCGTGTCC AGGAAGCCCTCCGGGCAG <u>G</u> CGTGTGCACGGTCGGTGAG AGTGGCGGGGTCGGCGCAGTTGGCTCCGCGCCGTGGAG	1398
	TGCACGAC <u>G</u> CTGCCCG	1399
	CCGGGCAG <u>G</u> CGTGTGCA	1400
10 Melanoma Arg87Pro CGG-CCG	GCGCGGAGGCCAACTGCGCCGACCCCGCCACTCTCACCGA CCCGTGACGAC <u>G</u> CTGCCGGGAGGGCTTCC GGTGGTGCTGCACCGGGCCGGGCGCGGCTGGACGTGCG	1401
	CGCACGTCCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAG CGTGTCCAGGAAGCCCTCCGGGCAGCGTGTGCACGGTC GGGTGAGAGTGGCGGGGTCGGCGCAGTTGGCTCCGCGC	1402
	CGCTGCCCGGGAGGGCT	1403
	AGCCCTCCGGGCAGCG	1404
15 Melanoma Arg87Trp cCGG-TGG	GGCGCGGAGGCCAACTGCGCCGACCCCGCCACTCTCACCG ACCCGTGCACGAC <u>G</u> CTGCCGGGAGGGCTTCC TGGTGGTGCTGCACCGGGCCGGGCGGGCTGGACGTGCG	1405
	GCACGTCCAGCCGCGCCCCGGCCCGGTGCAGCACCACCAGC GTGTCCAGGAAGCCCTCCGGGCAGCGTGTGCACGGGTGCG GGTGAGAGTGGCGGGGTCGGCGCAGTTGGCTCCGCGCC	1406
	ACGCTGCCCGGGAGGGC	1407
	GCCCTCCGGGCAGCGT	1408
15 Melanoma Leu97Arg CTG-CGG	CTCTCACCGACCGGTGCATGATGATGCTGCCGGGAGGGCTTC CTGGACACGCTGGTGGTG <u>C</u> TCACCGGGCCGGGCGCGGCT GGACGTGCGCGATGCCTGGGTGCTGTGCCGTGGACTT	1409
	AAGTCCACGGGCAGACGACCCCAGGCATCGCGCACGTCCAG CCGCGCCCCGGCCCGGT <u>C</u> GCACCAACCAGCGTGTCCAGGA AGCCCTCCGGGCAGCATCATGCACCGGTGGTGAGAG	1410
	GGTGGTGCT <u>G</u> ACCCGGG	1411

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	CCCGGTGCAGCACCACC	1412
Melanoma Arg99Pro CGG-CCG	CCCGACCGGTGCATGATGCTGCCCGGGAGGGCTTCTGGAC ACGCTGGTGGTGCACCGGGCCGGGGCGCGGCTGGACG TGCGCGATGCCTGGGTGCTCTGCCGTGGACTTGGCCGA	1413
	TCGGCCAAGTCCACGGGAGACGACCCCCAGGCATCGCGAC GTCCAGCCGCGCCCCGGCCGGTGCAGCACCACAGCGTGT CCAGGAAGCCCTCCCGGGCAGCATCATGCACCGGTGGG	1414
	GCTGCACCAGGGCCGGGG	1415
	CCCCGGCCCCGGTGCAGC	1416
Melanoma Gly101Trp cGGG-TGG	CCGGTGCATGATGCTGCCCGGGAGGGCTTCTGGACACGCT GGTGGTGCTGCACCGGGCCGGGGCGCGGCTGGACGTGCGC GATGCCTGGGTGCTCTGCCGTGGACTTGGCCGAGGAGC	1417
	GCTCCTCGCCAAGTCCACGGGAGACGACCCCCAGGCATCG CGCACGTCCAGCCGCGCCCCGGCCGGTGCAGCACCACAG CGTGTCCAGGAAGCCCTCCCGGGCAGCATCATGCACCGG	1418
	ACCGGGCCGGGGCGCGG	1419
	CCGCGCCCCGGCCCGT	1420
	CGGGAGGGCTTCTGGACACGCTGGTGGTGCACCGGGC CGGGGCGCGGCTGGACGTGCGCGATGCCTGGGTGCTCTGC CCGTGGACTTGGCCGAGGAGCGGGGCCACCGCGACGTTG	1421
Melanoma Arg107Cys gCGC-TGC	CAACGTGCGGGTGGCCCCGCTCTCGGCCAAGTCCACGGGC AGACGACCCCAGGCATCGCGCACGTCCAGCCGCGCCCCGGC CCGGTGCAGCACCACCAAGCGTGTCCAGGAAGCCCTCCCG	1422
	TGGACGTGCGCGATGCC	1423
	GGCATCGCGCACGTCCA	1424
	CACCGGGCCGGGGCGCGCTGGACGTGCGCGATGCCTGGG GCCGTCTGCCGTGGACCTGGCTGAGGAGCTGGGCCATCGC GATGTCGACGGTACCTGCGCGCGCTGCGGGGGCACCA	1425
Melanoma Ala118Thr gGCT-ACT	TGGTCCCCCGCAGCCGCGCGCAGGTACCGTGCACATCG CGATGGCCCAGCTCTCAGCCAGGTCCACGGGCAGACGGCC CCAGGCATCGCGCACGTCCAGCCGCGCCCCGGCCGGTG	1426
	TGGACCTGGCTGAGGAG	1427
	CTCCTCAGCCAGGTCCA	1428
	TGCGCGATGCCTGGGCCGTCTGCCGTGGACCTGGCTGAG GAGCTGGGCCATCGCGATGTCGCACGGTACCTGCGCGCGC TGCAGGGGGCACCAGAGGCAGTAACCATGCCCGCATAGA	1429
Melanoma Val126Asp GTC-GAC	TCTATGCCGGCATGGTTACTGCCTCTGGTGGGGGGCAGCC GCGCGCAGGTACCGTGCACATCGCGATGGCCCACCTCCTC AGCCAGGTCCACGGGCAGACGGCCCCAGGCATCGCGCA	1430
	TCGCGATGTCGCACGGT	1431

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	ACCGTGCG <u>A</u> ATCGCGA	1432

EXAMPLE 11
Adenomatous polyposis of the colon - APC

Adenomatous polyposis of the colon is characterized by adenomatous polyps of the colon and rectum; in extreme cases the bowel is carpeted with a myriad of polyps. This is a viciously premalignant disease with one or more polyps progressing through dysplasia to malignancy in untreated gene carriers with a median age at diagnosis of 40 years.

Mutations in the APC gene are an initiating event for both familial and sporadic colorectal tumorigenesis and many alleles of the APC gene have been identified. Carcinoma may arise at any age from late childhood through the seventh decade with presenting features including, for example, weight loss and inanition, bowel obstruction, or bloody diarrhea. Cases of new mutation still present in these ways but in areas with well organized registers most other gene carriers are detected. The attached table discloses the correcting oligonucleotide base sequences for the APC oligonucleotides of the invention.

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Table 18
APC Mutations and Genome-Correcting Oligos

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Arg121Term AGA-TGA	GGATCTGTATCAAGCCGTTCTGGAGAGTGCAGTCCTGTTCC ATGGGTTCAATTCCAAGA <u>A</u> GAGGGTTTGAAATGGAAGCAGA GAAAGTACTGGATATTAGAAGAACTTGAGAAAGAGA	1433
	TCTCTTCTCAAGTTCTAAATATCCAGTACTTCTGCTT CCATTACAAACCCCTCTCTGGAAATGAACCCATAGGAACAG GACTGCACTCTCCAGAACGGCTTGATACAGATCC	1434
	TTCCAAGA <u>A</u> GAGGGTT	1435
	AAACCCCTCTCTGGAA	1436
Adenomatous polyposis coli Trp157Term TGG-TAG	AAAAAAAAAATAGGTATTGCTTCTGCTGATCTTGACAAGAA GAAAAGGAAAAAGACT <u>GG</u> TATTACGCTCAACTTCAGAACTCA CTAAAAGAATAGATAGTCTTCCTTAACTGAAAA	1437
	TTTCAGTTAAAGGAAGACTATCTATTCTTTAGTGAGATTCTG AAGTTGAGCGTAATACC <u>AG</u> TCTTTCTCTTTGTCAA GATCAGCAAGAAGCAATGACCTATTTTTTT	1438
	AAAAGACT <u>GG</u> TATTACG	1439
	CGTAATACC <u>AG</u> TCTTT	1440
	AAATAGGTATTGCTTCTGCTGATCTTGACAAGAAGAAAAG GAAAAGACTGGTATTAC <u>G</u> GCTCAACTTCAGAACTCACTAAAA GAATAGATAGTCTTCCTTAACTGAAAATGTAAGT	1441
Adenomatous polyposis coli Tyr159Term TAC-TAG	ACTTACATTTCAAGTTAAAGGAAGACTATCTATTCTTTAGTGA GATTCTGAAGTTGAGCGTAATACCAGTCTTTCTCTTTCT TTGTCAGATCAGCAAGAAGCAATGACCTATTT	1442
	TGGTATTACGCTCAACT	1443
	AGTTGAGCGTAATACCA	1444
	TTGCTTCTGCTGATCTTGACAAGAAGAAAAGGAAAAGACT GGTATTACGCTCAACT <u>C</u> AGAACTCTCACTAAAAGAATAGATAG TCTTCCTTAACTGAAAATGTAAGTAACTGGCAGT	1445
	ACTGCCAGTTACTTACATTTCAAGTTAAAGGAAGACTATCTATT CTTTAGTGAGATTCT <u>G</u> AAGTTGAGCGTAATACCAGTCTTTCT CTTTCTTCTTGTCAGATCAGCAAGAAGCAA	1446
Adenomatous polyposis coli Gln163Term CAG-TAG	CTCAACT <u>C</u> AGAACTC	1447
	GAGATTCT <u>G</u> AAGTTGAG	1448
	CTTGACAAAGAAGAAAAGGAAAAGACTGGTATTACGCTAAC TTCAGAACTCACTAAA <u>AG</u> AATAGATAGTCTTCCTTAACTGAA AATGTAAGTA <u>CT</u> GGCAGTACAACCTATTGAAA	1449
	TTTCAAATAAGTTGACTGCCAGTTACTACATTTCAGTTAAA GGAAGACTATCTATT <u>C</u> TTTAGTGAGATTCTGAAGTTGAGCGT AATACCAGTCTTTCTCTTCTTGTCAG	1450

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TCACTAAA <u>AGAATAGAT</u>	1451
	ATCTATTCTTTAGTGA	1452
Adenomatous polyposis coli Ser171lle AGT-ATT	AAGAAAAGGAAAAAGACTGGTATTACGCTCAACTCAGAACATCT CACTAAA <u>AGAATAGATAGTCTCCCTTA</u> ACTGAAAATGTAAGTA ACTGGCAGTACAACCTATTGAAACTTTAATAAC	1453
	GTTATTAAAGTTCAAATAAGTTGACTGCCAGTTACTTACATT TTCAGTTAAAGGAAG <u>AGACTATCTATTCTTTAGT</u> GAGATTCTGAA GTTGAGCGTAATACCAGTCTTTCCCTTTCTT	1454
	AATAGATAGTCTCCCTT	1455
	AAGGAAG <u>ACTATCTATT</u>	1456
Adenomatous polyposis coli Gln181Term CAA-TAA	GATTAACGTAAATACAAGATATTGATACTTTTATTATTGTGG TTTAGTTTCCCT <u>ACAAACAGATATGACCAGAAGGCAATTGG</u> AATATGAAGCAAGGCAAATCAGAGTTGCGATGG	1457
	CCATCGCAACTCTGATTGCCTGCTTCATATTCCAATTGCCT TCTGGTCATATCTGTT <u>GTAAGGAAA</u> ACTAAAACCACAAATAAT AAAAAAAGTATCAATATCTTGTATTACGTTAAC	1458
	TTTCCTTACAAACAGAT	1459
	ATCTGTT <u>GTAAGGAAA</u>	1460
	CTTTTATTATTGTGGTTAGTTCCCTACAAACAGATATG ACCAAGGCAATTGGATATGAAGCAAGGCAAATCAGAGTT GCGATGGAAGAACAACTAGGTACCTGCCAGGATA	1461
Adenomatous polyposis coli Glu190Term GAA-TAA	TATCCTGGCAGGTACCTAGTTGTTCCATCGCAACTCTGAT TTGCCCTGCTTCATATT <u>CCAATTGCC</u> TTCTGGTCATATCTGTT GTAAGGAAA <u>ACTAAAACCACAAATAATAAAAAG</u>	1462
	GGCAATT <u>GGAAATATGAA</u>	1463
	TTCATATT <u>CCAATTGCC</u>	1464
	CAATTGGAAATATGAAGCAAGGCAAATCAGAGTTGCGATGGAA GAACA <u>ACTAGGTACCTGCC</u> CAGGATATGGAAAAACGAGCACAG GTAAGTTACTTGTTC <u>TAAGT</u> GATAAAACAGCGAAGA	1465
	TCTTCGCTTTTATCACTTAGAAACAAGTAAC <u>TTACCTGTGCT</u> CGTTTCCATATCT <u>GGCAGGTACCTAGTTGTTCC</u> CATCG CAACTCTGATTGCCCTGCTTCATATTCCAATTG	1466
Adenomatous polyposis coli Gln208Term CAG-TAG	GTACCTGCCAGGATATG	1467
	CATATCC <u>GGCAGGTAC</u>	1468
	GCAAGGCAAATCAGAGTTGCGATGGAAAGAACAACTAGGTACC TGCCAGGATATGGAAAAACGAGCACAG <u>GTAA</u> GTACTTGTTC TAAGT <u>GATAAAACAGCGAAGAGCTATTAGGAATAAA</u>	1469
	TTTATTCC <u>TAAGCTT</u> CGCTGTTTATCACTTAGAAACAAG TAAC <u>TTACCTGTGCTCG</u> TTTCCATATCCTGGCAGGTACCTA GTTGTTCTCCATCGCAACTCTGATT <u>GCCTTG</u> C	1470
	TGGAAAAACGAGCACAG	1471
Adenomatous polyposis coli Arg213Term CGA-TGA	CTGTGCT <u>CGTTTCCA</u>	1472

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Arg232Term CGA-TGA	GTTTTATTTAGCGAAGAATAGCCAGAATTCAAGCAAATCGAAA AGGACATACTCGTATACGACAGCTTTACAGTCCCAGAAC AGAAGCAGAGGTTAGTAAATTGCCCTTCTTGTITG	1473
	CAAACAAGAAAGGCAATTACTAACCTCTGCTTCTGTTGCTTG GGACTGTAAAAGCTGTCGTATACGAAGTATGTCCTTTGATT TGCTGAATTCTGGCTATTCTCGCTAAAATAAAC	1474
	TTCGTATACGACAGCTT	1475
	AAGCTGTCGTATACGAA	1476
Adenomatous polyposis coli Gln233Term CAG-TAG	TTATTTAGCGAAGAATAGCCAGAATTCAAGCAAATCGAAAAGG ACATACTTCGTATACGACAGCTTTACAGTCCCAGAACAGA AGCAGAGGTTAGTAAATTGCCCTTCTTGTITGTTG	1477
	CCACAAACAAGAAAGGCAATTACTAACCTCTGCTTCTGTTGC TTGGGACTGTAAAAGCTGTCGTATACGAAGTATGTCCTTTG ATTGCTGAATTCTGGCTATTCTCGCTAAAATAA	1478
	GTATACGACAGCTTTA	1479
	TAAAAGCTGTCGTATAC	1480
Adenomatous polyposis coli Gln247Term CAG-TAG	AGAAAGCCTACACCATTTCGCATGTACTGATGTTAACTCCAT CTTAACAGAGGTATCTCAGAACAGCATGAAACCGGGCTCAC ATGATGCTGAGCGGGAGAACATGAAGGTCAAGGAGTGG	1481
	CCACTCCTGACCTTCATTCTGCCGCTCAGCATCATGTGAGC CGGTTTCACTGCTTCTGAGATGACCTCTGTTAAGATGGAGT TAACATCAGTACATGAAAAATGGTAGGCTTCT	1482
	GGTCATCTCAGAACAAAG	1483
	CTTGTCTGAGATGACC	1484
Adenomatous polyposis coli Gly267Term GGA-TGA	CAGAACAAAGCATGAAACCGGCTCACATGATGCTGAGCGGCAG AATGAAGGTCAAGGAGTGGGAGAACATCAACATGGCAACTTCT GGTAATGGTCAGGTAAATAATTATTTATCATATT	1485
	AAATATGATAAAATAATTATTCACCTGACCATTACCAAGATT GCCATGTTGATTTCTCCCACTCCTGACCTTCATTCTGCCGCT CAGCATCATGTGAGCCGGTTCATGCTTCTG	1486
	AAGGAGTGGGAGAACATC	1487
	GATTCTCCCACTCCTT	1488
Adenomatous polyposis coli Glu443Term GAA-TAA	CTTCAAATAACAAAGCATTATGGTTATGTTGATTTATTTCA GTGCCAGCTCTGTTGAACATCAGATCTGCTCTGCTGTGT GTTCTAATGAAACTTCATTGATGAAGAGCATA	1489
	TATGCTCTCATCAAATGAAAGTTCTTGAACACACACAGCA GGACAGATCTGATGTTCAACAGGAGCTGGCACTGAAAAATAA AATCAACATAAACCTATAATGCTTGTATTGAAG	1490
	CTCCTGTTGAACATCAG	1491
	CTGATGTTCAACAGGAG	1492
Adenomatous polyposis coli SER457TER TCA-TAA	CAGTGCCAGCTCCTGTTGAACATCAGATCTGCTCTGCTGT GTGTTCTAATGAAACTTCATTGATGAAGAGCATAAGACATGC AATGAATGAACAGGTAAGACAAAAATGTTTTAA	1493

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TTAAAAAACATTTGTCTTACCTAGTCATTGATGTCTA TGCTCTTCATCAAAT <u>GAAAGTT</u> CATTAGAACACACACAGCAG GACAGATCTGATGTTAACAGGAGCTGGCACTG	1494
	<u>GAAACTTC</u> ATTTGATG	1495
	CATCAAAT <u>GAAAGTT</u> C	1496
Adenomatous polyposis coli Gln473Term CAG-TAG	AGTTGTTTATTTAGATGATTGCTTTCCCTTGCCCCTTTT AAATTAGGGGGACTAC <u>AGGCCATTG</u> CAGAATTATTGCAAGTG GAAGTGTGAAATGTACGGGCTTAATGACCAC	1497
	AGTGGTCATTAGTAAGCCGTACATTCACAGTCCACTGCAA TAATTCTGCAATGGCCT <u>G</u> TAGTCCCCCTAATTAAAAGGGCA AGAGGAAAAAGACAATCATCTAAAATAAAACAAC	1498
	GGGGACTACAGGCCATT	1499
	AATGGCCT <u>G</u> TAGTCCCC	1500
Adenomatous polyposis coli Tyr486Term TAC-TAG	TTTTAAATTAGGGGGACTACAGGCCATTGCAGAATTATTGCAA GTGGACTGTGAAATGTAC <u>GGGCT</u> TAATGACCACACAGTA TTACACTAAGACGATATGCTGGAATGGCTTGACA	1501
	TGTCAAAGCCATTCCAGCATATCGTCTTAGTGTAAACTGTAG TGGTCATTAGTAAGCC <u>G</u> TACATTCACAGTCCACTGCAATA ATTCTGCAATGGCCTGTAGTCCCCCTAATTAAA	1502
	GAAATGTAC <u>GGGCT</u> TAC	1503
	GTAAGCCGTACATTTC	1504
Adenomatous polyposis coli Arg499Term CGA-TGA	TTGCAAGTGGACTGTGAAATGTATGGGCTTACTAATGACCACT ACAGTATTACACTAAGAC <u>G</u> ATATGCTGGAATGGCTTGACAAA CTTGACTTTGGAGATGTAGCCAACAAGGTATGTT	1505
	AACATACCTTGTGGCTACATCTCCAAAAGTCAGTTGTCAA AGCCATTCCAGCATATCGTCTTAGTGTAAACTGTAGTGGTCA TTAGTAAGCCCACATTCACAGTCCACTGCAA	1506
	CACTAAGACGATATGCT	1507
	AGCATATCGTCTTAGTGT	1508
Adenomatous polyposis coli Tyr500Term TAT-TAG	AGTGGACTGTGAAATGTATGGGCTTACTAATGACCACTACAGT ATTACACTAAGACGATATGCTGGAATGGCTTGACAAACTTGA CTTTGGAGATGTAGCCAACAAGGTATGTTTTAT	1509
	ATAAAAACATACCTTGTGGCTACATCTCCAAAAGTCAGTTG TCAAAGCCATTCCAG <u>C</u> ATATCGTCTTAGTGTAAACTGTAGTG GTCATTAGTAAGCCACATTCACAGTCCACT	1510
	AGACGATATGCTGGAAT	1511
	ATTCCAG <u>C</u> ATATCGTCT	1512
Adenomatous polyposis coli Lys586Term AAA-TAA	GACAAATCCAACTCTAATTAGATGACCCATATTCTGTTCTTA CTAGGAATCAACCC <u>T</u> AAAGCGTATTGAGTGCCTTATGGAAT TTGTCAGCACATTGCACTGAGAATAAGCTGATA	1513
	TATCAGCTTATTCTCAGTGCATGTGCTGACAAATTCCATAA GGCACTCAATACGCTTT <u>G</u> AGGGTTGATTCTAGTAAGAAACA GAATATGGGTACATCTAATTAGAGTTGGAATTGTC	1514
	CAACC <u>C</u> TT <u>AAAAGCGT</u> A	1515

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
	TACGCTTTGAGGGTTG	1516
Adenomatous polyposis coli Leu592Term TTA-TGA	TAGATGACCCATATTCTGTTTCACTAGGAATCAACCCTCAA AGCGTATTGAGTCGCCTATGAAATTGTCAAGCACATTGCACTG AGAATAAAGCTGATATATGTGCTGTAGATGGTGC	1517
	GCACCATCTACAGCACATATATCAGCTTATTCTCAGTGCAAT GTGCTGACAAATTCCATAAGGCACACTAACAGCTTTGAGGGT TGATTCCCTAGTAAGAACAGAAATATGGGTCACTCA	1518
	GAGTGCCTTATGGAATT	1519
	AATTCCATAAGGCACTC	1520
Adenomatous polyposis coli Trp593Term TGG-TAG	ATGACCCATATTCTGTTTCACTAGGAATCAACCCTCAAAG CGTATTGAGTCGCCTTATGAAATTGTCAAGCACATTGCACTGAG ATAAAAGCTGATATATGTGCTGTAGATGGTGCAC	1521
	AGTGCACCATCTACAGCACATATATCAGCTTATTCTCAGTG AATGTGCTGACAAATTCCATAAGGCACACTAACAGCTTTGAG GGTTGATTCCCTAGTAAGAACAGAAATATGGGTCA	1522
	TGCCTTATGGAATTGT	1523
	ACAAATTCCATAAGGC	1524
Adenomatous polyposis coli Trp593Term TGG-TGA	TGACCCATATTCTGTTTCACTAGGAATCAACCCTCAAAGC GTATTGAGTCGCCTTATGAAATTGTCAAGCACATTGCACTGAGA ATAAAAGCTGATATATGTGCTGTAGATGGTGCAC	1525
	AAGTGCACCATCTACAGCACATATATCAGCTTATTCTCAGTG CAATGTGCTGACAAATTCCATAAGGCACACTAACAGCTTTGA GGGTTGATTCCCTAGTAAGAACAGAAATATGGGTCA	1526
	GCCTTATGGAATTGTG	1527
	GACAAATTCCATAAGGC	1528
Adenomatous polyposis coli Tyr622Term TAC-TAA	TAAAGCTGATATATGTGCTGTAGATGGTGCACITGCATTTTG GTTGGCACTCTTACTTACCGGAGCCAGACAAACACTTAGCC ATTATTGAAAGTGGAGGTGGGATATTACGGAATGTG	1529
	CACATTCCGTAATATCCCACCTCCACTTCAATAATGGCTAAA GTGTTGCTGGCTCCGGTAAGTAAGAGTGCCACCAAAAAAT GCAAGTGCACCATCTACAGCACATATATCAGCTTA	1530
	CTTACTTACCGGAGCCA	1531
	TGGCTCCGGTAAGTAAG	1532
Adenomatous polyposis coli Gln625Term CAG-TAG	GATATATGTGCTGTAGATGGTGCACITGCATTTGGTGGCA CTCTTACTTACCGGAGCCAGACAAACACTTAGCCATTATTGA AAGTGGAGGTGGGATATTACGGAATGTGTCAGCT	1533
	AGCTGGACACATCCGTAATATCCCACCTCCACTTCAATAAT GGCTAAAGTGTGCTGGCTCCGGTAAGTAAGAGTGCCAC AAAAATGCAAGTGCACCATCTACAGCACATATATC	1534
	ACCGGAGCCAGACAAAC	1535
	GTGTTGCTGGCTCCGGT	1536

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Leu629Term TTA-TAA	TAGATGGTGCAC T GCATTGGTGGCACTCTACTAACCG GAGCCAGACAAACACT T AGCCATTATTGAAAGTGGAGGTGG GATATTACGGAATGTGTCCAGCTTGATAGCTACAAA	1537
	TTTAGCTATCAAGCTGGACACATTCCGTAATATCCCACCTC CACTTCATAATGGCTAAAGTGTGTCTGGCTCCGGTAAGT AAGAGTGCCAACAAAAATGCAAGTGCACCACATCTA	1538
	AAACACTTAGCCATT	1539
	TAATGGCTAAAGTGT	1540
Adenomatous polyposis coli Glu650Term GAG-TAG	GCCATTATTGAAAGTGGAGGTGGATATTACGGAATGTGTCC AGCTTGATAGCTACAAATGAGGACACAGGTATATAGAGTT TTATATTACTTTAAAGTACAGAATTCAACTCTCA	1541
	TGAGAGTATGAATTCTGTACTTTAAAGTAATATAAAACTCTAT ATATACCTGTGGTCCTCATTTGTAGCTATCAAGCTGGACACAT TCCGTAATATCCCACCTCCACTTCAATAATGGC	1542
	CTACAAATGAGGACAC	1543
	GTGGTCCTCATTTGTAG	1544
Adenomatous polyposis coli Trp699Term TGG-TGA	TGCATGTGGAAC T TGTGGAATCTCTCAGCAAGAAATCTAAA GACCAGGAAGCATTATGGGACATGGGGCAGTTAGCATGCTC AAGAACCTCATTCAAAAGCACAAATGATTGCT	1545
	AGCAATCATTGTGCTTGAATGAATGAGGTCTTGAGCATG CTAACTGCCCATGTCCCATAATGCTTCTGGCTTCTAGGAT TTCTGCTGAGAGATTCCACAAAGTCCACATGCA	1546
	GCATTATGGGACATGGG	1547
	CCCATGTCCCATAATGCA	1548
Adenomatous polyposis coli Ser713Term TCA-TGA	AAGACCAGGAAGCATTATGGGACATGGGGCAGTTAGCATGC TCAAGAACCTCATTCAAAAGCACAAATGATTGCTATGGG AAGTGCTGCAGCTTAAGGAATCTCATGGCAAATAG	1549
	CTATTGCCATGAGATTCTTAAAGCTGCAGCAGCTCCATAG CAATCATTGTGCTTGAATGAATGAGGTCTTGAGCATGCT AACTGCCCATGTCCCATAATGCTTCTGGCTT	1550
	CATTCAAAAGCACA	1551
	TGTGCTTGAATGAATG	1552
Adenomatous polyposis coli Ser722Gly AGT-GGT	GGGGCAGTTAGCATGCTCAAGAACCTCATTCAAAAGCAC AAAATGATTGCTATGGGAAGTGCTGCAGCTTAAGGAATCTCA TGGCAAATAGGCCTGCGAAGTACAAGGATGCCAATA	1553
	TATTGGCATCCTGTACTTCGCAGGCCTATTGCCATGAGATT CCTTAAAGCTGCAGCAC T CCCATAGCAATCATTGTGCTT GAATGAATGAGGTCTTGAGCATGCTAACTGCC	1554
	CTATGGGAAGTGCTGCA	1555
	TGCAGGCACTCCCATAG	1556

Clinical Phenotype & Mutation	Correcting Oligos	SEQ ID NO:
Adenomatous polyposis coli Leu764Term TTA-TAA	TCTCCTGGCTCAGCTGCCATCTTCATGTTAGGAAACAAAA AGCCCTAGAACGAGAA <u>T</u> AGATGCTCAGCACTTATCAGAAACT TTTGACAATATAGACAATTAAAGTCCCAGGCATC	1557
	GATGCCTGGGACTAAATTGTCTATATTGTCAAAAGTTCTGA TAAGTGCTGAGCATCT <u>A</u> ATTCTGCTTAGGGCTTTGTTTC CTAACATGAAGAGATGGCAAGCTGAGCCAGGAGA	1558
	AGCAGAATTAGATGCTC	1559
	GAGCATCT <u>A</u> ATTCTGCT	1560
Adenomatous polyposis coli Ser784Thr TCT-ACT	TTAGATGCTCAGCACTTATCAGAAACTTTGACAATATAGACAA TTTAAGTCCCAGGCATCTCATCGTAGTAAGCAGAGACACAG CAAGTCTCTATGGTGATTATGTTTGACACCATC	1561
	GATGGTGTCAAAACATAATCACCATAGAGACTGCTGTCT CTGCTTACTACGATGAG <u>A</u> TGCCCTGGGACTAAATTGTCTATA TTGTCAAAAGTTCTGATAAGTGTGAGCATCTAA	1562
	CCAAGGCATCTCATCGT	1563
	ACGATGAG <u>A</u> TGCCCTGG	1564
Adenomatous polyposis coli Arg805Term CGA-TGA	CTCATCGTAGTAAGCAGAGACACAGCAAGTCTCTATGGTATT ATGTTTTGACACCAAT <u>C</u> GACATGATGATAATAGGTAGACAT TTAATACTGGCACATGACTGTCCTTCACCATAT	1565
	ATATGGTGAAGGACAGTCATGTGCCAGTATTAATGTCTGA CCTATTATCATCATGTC <u>G</u> ATTGGTGTCAAAACATAATCACCAT AGAGACTTGCTGTCTCTGCTTACTACGATGAG	1566
	ACACCAAT <u>C</u> GACATGAT	1567
	ATCATGTC <u>G</u> ATTGGTGT	1568
Adenomatous polyposis coli Gln879Term CAG-TAG	GGTCTAGGCAACTACCACATCCAGCAACAGAAAATCCAGGAAC TCTTCAAAGCGAGGTTG <u>C</u> AGATCTCCACCACTGCAGCCCAG ATTGCCAAAGTCATGGAAGAAGTGTCAGCCATTATA	1569
	TATGAATGGCTGACACTTCTCCATGACTTGGCAATCTGGC TGCAGTGGTGGAGATCT <u>G</u> CAAACCTCGTTGAAGAAGTTCC TGGATTITCTGTTGCTGGATGGTAGTTGCCTAGACC	1570
	GAGGTTTG <u>C</u> AGATCTCC	1571
	GGAGATCT <u>G</u> CAAACCTC	1572
Adenomatous polyposis coli Ser932Term TCA-TAA	TACATTGTGTGACAGATGAGAGAAATGCACTTAGAAGAAGCTC TGCTGCCCATACACATT <u>C</u> AAACACTTACAATTCAACTAGTCG GAAAATTCAAATAGGACATGTCCTATTGAATTTCGACTTAG	1573
	GCATAAGGCATAGAACATGTCCTATTGAATTTCGACTTAG TGAAATTGTAAGTGT <u>T</u> GAATGTGTATGGCAGCAGAGCTCT TCTAAGTGCATTCTCATCTGTACACACAATGTA	1574
	TACACATT <u>C</u> AAACACTT	1575
	AAGTGT <u>T</u> GAATGTGT	1576
Adenomatous polyposis coli Ser932Term TCA-TGA	TACATTGTGTGACAGATGAGAGAAATGCACTTAGAAGAAGCTC TGCTGCCCATACACATT <u>C</u> AAACACTTACAATTCAACTAGTCG GAAAATTCAAATAGGACATGTCCTATTGAATTTCGACTTAG	1577